

AAPS Introductions in the Pharmaceutical Sciences

Dimitrios A. Lamprou *Editor*

3D & 4D Printing Methods for Pharmaceutical Manufacturing and Personalised Drug Delivery

Opportunities and Challenges



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Dimitrios A. Lamprou
Editor

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Opportunities and Challenges

Editor

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Preface

Additive manufacturing (AM) or 3D printing (3DP) involves new technologies that allow the creation of three-dimensional (3D) objects based on a computer-aided design (CAD) model. The technique makes possible the manufacturing of prototypes that traditionally take months, to be completed in a matter of days or hours, saving both time and money. Over the past decade, 3D printing has transformed many industries and is one of the foundations of the fourth industrial revolution. This is because it offers unique advantages in manufacturing, over traditional methods, especially in the pharmaceutical sector. With personalised pharmaceutical forms, flexible dosages forms can be prepared with different shapes, multiple active pharmaceutical ingredients (APIs), and modulated release kinetics. Unlike conventional medicine, which uses a one-size-fits-all approach, personalised and precision medicine focuses on patient-centred treatments that takes into account individuals, including genetics, lifestyle, and pharmacokinetics, and has shown improved results compared to conventional approaches. One of the main features of 3D printing is that it is easy to be customised and, most importantly, is a sustainable method. The potential use of different materials helps to choose the most suitable one according to the desired final product and 3D printing technique employed.

3D printing is a technology that can be used to manufacture dosage forms, and especially formulations for paediatric and geriatric drug delivery, as allows the fabrication of high degrees of complexity with great reproducibility, in a fast and cost-effective fashion, and offers a new paradigm for the direct manufacture of personalised dosage forms. The book covers the basics of each additive manufacturing method, current applications in pharmaceuticals discussing the advantages and limitations of various 3D printing methods, includes case studies from an educational perspective aimed at undergraduate (UG) and postgraduate (PG) students, and cases for new researchers in the field, or experts that it might experiencing issues that can be possible solved by reading some of the specialised chapters covered in the book. Unique to this book is the integration of studies based upon the use of different additive manufacturing technologies, which designed to reinforce important printing

parameters and material considerations. The book includes case studies or multiple-choice questions (MCQs), which allow application of the content in a flipped-classroom.

The book starts with a general background information on 3D printing and the importance in the pharmaceutical field, covering also a dynamic form of printing, the four-dimensional (4D) printing. The first chapters are summarising the history of 3D and 4D printing and provide an overview on their use in personalised medicine, and covers the recent advancements in the field, including the implementation of the technique in the clinic, and the manufacturing of solid dosage forms (e.g. tablets, polypills, complex designs). Despite the advantages offered by 3D printing, there is still a lack of pharmaceutical-grade raw materials suitable for 3D printing; therefore, it is important to have a guide supporting the user choosing any starting material by having in mind the printing method that is planning to use. The reader will also learn about the regulatory considerations, especially the current standards for the manufacturing of oral dosage forms and implants, and walk through the practical considerations when implementing quality-by-design (QbD) into the innovative product design.

Another important aspect that the book deals with is the materials used in 3D printing, since the form and properties must be in accordance with the functional principle of the process, which determines the material choice in the development of pre-formulations for the manufacturing of drug delivery systems. Moreover, the guidelines for developing a protocol for pre-formulation studies of different 3D-printable drug delivery systems are also included.

The book includes individual chapters that are focusing on different 3D printing methods and how they can be used to prepare drug delivery systems and medical implants. Vat photopolymerisation (VP) a family of 3D printing technologies based on the photopolymerisation of liquid-light curing resins and the used in pharmaceuticals is a method that used for the manufacturing of microneedles, oral dosage forms, and other drug delivery systems. In addition, extrusion-based 3D printing (e.g. fused deposition modelling – FDM, direct powder extrusion – DPE, and semi-solid extrusion – SSE), one of the most studied approaches for the manufacturing of oral solid dosage forms with complicated features, has also been discussed in detail in the book. The basic principles of binder jetting (BJT) 3D printing, material formulation, and properties of the 3D-printed dosage forms, together with several key technical challenges, have also been covered. Selective laser sintering (SLS) is a powder-based 3D printing technology, and the combination of powder raw material and heat-based melting mechanism makes this printing method a very interesting technology for the manufacturing of drug delivery systems and medical devices. Of course, it is not possible to discuss also the various techniques of bioprinting as well as the most popular bioinks currently used, followed by the implementation of 4D printing that allows printed structures to change their form independently over time when exposed in specific temperature, pH, light, or radiation. The book concludes with a discussion of the various physicochemical methods that can be used to characterise the final 3D-printed products.

We hope that the chapters covered in this book will be helpful and will provide you with the information needed during your studies or research, or inspire you to start using 3D and 4D printing in your research for first time.

Belfast, UK

Dimitrios A. Lamprou

About the Book

New materials and manufacturing techniques are emerging with potential to address the challenges associated with the manufacture of pharmaceutical systems that will teach new tricks to old drugs. 3D printing (3DP) is a technique that can be used for the manufacturing of dosage forms, and especially targeting paediatric and geriatric formulations, as it permits the fabrication of high degrees of complexity with great reproducibility, in a fast and cost-effective fashion, and offers a new paradigm for the direct manufacture of personalised dosage forms. The book is covering the basics behind each additive manufacturing (AM) method, current applications in pharmaceuticals for each 3DP method, and case studies (examples) from a teaching perspective, targeting undergraduate (UG) and postgraduate (PG) students. A unique feature of this book is the integration of studies based upon the use of different AM technologies, which are designed to reinforce important printing parameters and material considerations. The book includes case studies or multiple-choice questions (MCQs), which allow application of the content in a flipped-classroom.

Key Features

- One book covering all advanced methods of 3D printing.
- Authors are pioneers and world leaders.
- 3D and 4D printing case studies for teaching UG and PG students.

Readership: Researchers in Industry and Academia that would like to learn the fundamentals of additive manufacturing for the manufacturing of drug delivery systems. Undergraduate and postgraduate students in Pharmacy, Pharmaceutical Sciences, Biotechnology, and Bioengineering will find this book very interesting.

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About the Editor

Dimitrios A. Lamprou (Ph.D. MBA) is a Full Professor (Chair) of Biofabrication and Advanced Manufacturing at Queen's University Belfast. Dimitrios has been recognised as world leader in Printing, with PubMed-based algorithms placed him currently in the top 0.047% of scholars in the world writing about Printing in the last 10 years. He is currently the author of over 140 peer-reviewed publications and of over 350 conference abstracts, and has over 140 Oral Talks in institutions and conferences across the world. His research and academic leadership have recognised in a range of awards, including the Royal Pharmaceutical Society of Great Britain Science Award and the Scottish Universities Life Sciences Alliance Leaders Scheme Award.

Chapter 1

3D and 4D Printing in Digital Healthcare



Atheer Awad and Abdul W. Basit

Abstract Three-dimensional (3D) printing is a digital manufacturing system that is transforming pharmaceutical production by empowering patients to play an active role in the treatment process. Along with its dynamic form, namely, four-dimensional (4D) printing, this technology can challenge boundaries across industries. Within healthcare, their digital features make them well suited for designing and formulating countless drug products with properties personalised to the needs and preferences of individual patients. Although not fully embraced, it has been predicted that 3D printing would work in synchronisation with other cyber technologies, giving rise to a modern healthcare era based on continuous patient care. This book chapter will summarise the history of 3D and 4D printing and provide an insight on their use for personalised medicine. This will be followed by a futuristic vision of its role in a modern digital healthcare model.

Keywords Digitised health and industry 4.0 · Pharmacy or Pharma 4.0 · Additive manufacturing · Tailored dosage forms and medications · Personalized drug products · Biomedical engineering and medical devices · 3D-printed formulations · Tailored therapeutics and precision medicine · On-demand dispensing and drug manufacturing · Patient-centred smart health · Medical care

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1 Introduction

In recent years, the industrial world has experienced a technological boom marked by the emergence of digital systems, reinvigorating the healthcare industry (Andreadis et al. 2022; Trenfield et al. 2022). State-of-the-art digital technologies are constantly being embraced at each phase of the drug development process, from lead discovery and identification all the way to post-market monitoring (Awad et al. 2021a). With such tools within reach, patient treatments are moving away from conventional one-size-fits-all approaches towards personalised medications that meet distinct patient requirements. The need for this shift stems from the fact that current mass manufacturing tactics are resulting in medications being inefficacious in up to ~70% of patients (National Health Service (NHS) in England 2016). Whilst personalising medications to the individual is an ideal solution, such medicines cannot be flexibly or efficiently produced under current healthcare models or using traditional manufacturing methods. Instead, this calls for the need to adopt a novel healthcare framework and the employment of trailblazing cyber technologies.

Three-dimensional (3D) printing refers to a set of additive manufacturing methods that create 3D objects of different shapes and sizes based on virtual designs or digital scans (Awad et al. 2023a). Owing to its multi-faceted and automated attributes, 3D printing is becoming the latest avant-garde technology within healthcare, permitting the fabrication of bespoke medicines, implants, prosthetics, and medical devices (Rodríguez-Pombo et al. 2022a; Karavasili et al. 2022; Yang et al. 2021; Vivero-Lopez et al. 2021; Xu et al. 2021a, b; Goh et al. 2021). Its distinct features allow it to be used for dispensing treatments at the point-of-care, at homes or in remote locations, permitting rapid and safer interventions. Being an all-in-one system, it is envisioned that perhaps in the future, this technology could even be used for swift screening of new lead compounds and their testing for intraindividual therapeutic responses using 3D bio-printed tissues and organs. Similarly, it can be used for small-scale production in preclinical and clinical testing, where frequent dose, size and geometry modification are needed.

With the introduction of four-dimensional (4D) printing, the possibilities with 3D printing are pushing the boundaries of imagination and creativity now more than ever. This modern technique equips 3D objects with dynamic attributes, allowing therapies to be fine-tuned to precisely deliver drugs to the site of action in ways not possible to achieve using traditional approaches. This chapter will provide a comprehensive overview on the history of 3D printing; its most recent innovations within pharmacy and healthcare, covering its up-to-date and prospective applications in drug delivery and medicine; as well as the impact and potential of 4D printing in healthcare.

2 History

The concept of 3D printing was first originated in 1945 in the novelette *Things Pass By*. The sci-fi author, Murray Leinster, portrayed a device that uses a drawing arm that melts plastics to create objects from scanned drawings. The idea remained hypothetical until 1981 when a Japanese inventor, Hideo Kodama, developed a “stereoscopic figure

drawing device” that uses an ultraviolet (UV) light source to polymerise a photoresponsive liquid resin (Kodama 1981). Although Kodama filed his patent application, his lack of funding resulted in the patent abandonment. Later in 1984, three French inventors, Jean-Claude André, Olivier de Witte and Alain le Méhauté, filed a patent for a “device for producing an industrial part model” (Andre et al. 1984). Nevertheless, their invention was also abandoned due to the absence of funds.

The advent of 3D printing is mostly credited to Charles Hull, who is referred to as the father of the technology. His patent for an “apparatus for the production of three-dimensional objects by stereolithography” was filed in 1984, just 3 weeks after the French Trio. Unlike the previous attempts, Hull’s patent on stereolithography (SLA) was granted in 1986 (Hull 1986), with his invention being commercialised 2 years later. This milestone paved the way for other 3D printing technologies in the following years, including the invention of fused deposition modelling (FDM) by Scott Crump (Crump 1992) and selective laser sintering (SLS) by Carl Deckard, both in 1988 (Deckard 1989).

The term 3D printing was not coined until 1993, when Emanuel Sachs, a Professor at Massachusetts Institute of Technology (MIT), invented his inkjet technology (Sachs et al. 1993). With the growing interest in 3D printing, the following years saw further advancements in the technology. As an example, in 2000, ZCorp introduced their multicolour 3D printing system which repurposes inkjet printing to colour 3D objects (3D Sourced 2021). Later in 2004, Adrian Bowyer introduced the RepRap concept which uses existing 3D printers to create other 3D printers (Jones et al. 2011). In 2006, Objet commercialised their first desktop 3D printer, introducing at-home 3D printers to the public (3D Sourced 2021). The technology made its way to the food industry, with the first 3D food printer being launched in 2007 by researchers at Cornell University (McHugh 2017). To further support this notion, Thingiverse was founded in 2008, permitting individuals to exchange 3D designs and print ideas (Baichtal 2008). With 3D printing’s soaring popularity, many world-leading companies began launching 3D printers, including Hewlett-Packard (HP) (Hewlett-Packard 2016) and General Electric (GE) (Kellner 2018) since 2016.

2013 saw the first mention of the term “4D printing” by Skylar Tibbits during his Technology, Entertainment, Design (TED) talk (Tibbits 2013). The MIT Associate Professor demonstrated how computational modelling can be used to design self-changing structures (Raviv et al. 2014). The structures were created using multi-materials and consisted of two parts – a dynamic and rigid one. The dynamic region was water-responsive, allowing the structure to regain its shape when exposed to water.

3 Types of 3D Printing Systems

The International Organisation for Standardisation (ISO) and American Society for Testing and Materials (ASTM) recognise seven main classes of 3D printing technologies; namely, material extrusion, material jetting, powder bed fusion, binder

jetting, vat photopolymerisation, sheet lamination and directed energy deposition (International Organization for Standardization: ISO/ASTM 52900:2021 [2021](#)). These technologies share the common attribute of following a layer-by-layer fashion but differ in their consolidation mechanism, type of feedstock used (e.g. thermoplastics, pastes, ceramics, metals or resins) and/or final product properties (i.e. surface finish, texture, geometry and/or mechanical strength). As a result, they can produce a variety of products for different applications (e.g. prototyping, fashionwear, food or automobiles (Barnatt [2013](#), [2016](#); Ventola [2014](#); Chowdry [2013](#); Yun et al. [2023](#); Wilson et al. [2020](#))).

3.1 *Material Extrusion*

Material extrusion refers to processes that selectively dispense semi-molten material by heating them through an orifice (Seoane-Viaño et al. [2021a](#)). This umbrella term is often subdivided into (1) FDM, which utilises thermoplastics formed into spools of filaments that are typically created using hot melt extrusion; and (2) semi-solid extrusion (SSE), which utilises gels, waxes and pastes that are formed prior to printing and filled into syringes suitable for printing (Awad et al. [2018a](#); Seoane-Viaño et al. [2021b](#); Díaz-Torres et al. [2022](#)). More recently, a new stratification, namely, direct powder extrusion (DPE) (also known as melt extrusion deposition (MEDTM)), was introduced (Zheng et al. [2021](#); Ong et al. [2020](#)). This process employs powder materials as its feedstock, reducing risks of drug degradation by limiting its exposure to heat by simplifying the printing procedure into a single-step method (Zheng et al. [2021](#); Ong et al. [2020](#); Fanous et al. [2020](#); Goyanes et al. [2019a](#)).

3.2 *Material Jetting*

Material jetting refers to processes that form objects by selectively depositing liquid droplets of materials onto a surface (Gülcan et al. [2021](#); Gibson et al. [2015a](#)). In the drop-on-demand (DOD) process, the droplets spontaneously consolidate; alternatively they are cured or fuse using a UV light source in the polyjet process or using a heat source in the nanoparticle jetting (NPJ) process.

3.3 *Powder Bed Fusion*

Powder bed fusion refers to thermal processes that selectively fuse powder particles using an energy source (Awad et al. [2020a](#)). It encompasses SLS, where a laser source is used to sinter (i.e. superficially melt the surface) thermoplastic polymer

particles together; multijet fusion (MJF), where an infrared lamp is used for the consolidation of thermoplastic polymers; direct metal laser sintering (DMLS) and selective laser melting (SLM), where a laser beam is used to consolidate single component metal (in the case of SLM) and metal alloys powders (in the case of DMLS); and electron beam melting (EBM), where an electron beam is directed over metal and alloyed powders to consolidate them (Awad et al. [2021b](#)).

3.4 Binder Jetting

Binder jetting (also known as inkjet printing) refers to the binding of powder particles by selectively scattering a liquid agent on their surface (Gokuldoss et al. [2017](#); Gibson et al. [2015b](#)).

3.5 Vat Photopolymerisation

Vat photopolymerisation refers to processes that selectively consolidate a vat of liquid photopolymers using a light source (Xu et al. [2021c](#)). Examples of such are SLA, where a laser beam is used; digital light processing (DLP), where the light source is a digital light projector; liquid crystal display (LCD), where the consolidation is initiated using a UV light generated from an array of light-emitting diodes (LEDs) passing through an LCD screen; and two-photon polymerisation (2PP), where a titanium sapphire femtosecond laser is employed. The continuous liquid interface production (CLIP) technology was introduced based on the fundamentals of the DLP technology, with the addition of an oxygen-permeable window, creating a “dead zone” that increases its production throughput (Bloomquist et al. [2018](#)). More recently, the volumetric printing technology was launched to allow objects to be created within seconds by avoiding the layer-by-layer approach, making it the fastest 3D printing technology to date (Rodríguez-Pombo et al. [2022a](#), [2023](#)).

3.6 Sheet Lamination

Sheet lamination refers to processes that consolidate sheets of materials to fabricate 3D objects. To date, seven subclassifications of this technology exist (Engineering Product Design: Sheet Lamination [2023](#)): laminated object manufacturing (LOM), where sheets of paper are used as the feedstock; selective lamination composite object manufacturing (SLCOM), where carbon and aramid fibres, fiberglass, poly (p-phenylene-2,6-benzobisoxazole) (PBO, e.g. Zylon) and metal fibres (e.g. steel, aluminium or titanium) are used; plastic sheet lamination (PSL), where polymer

sheets are employed; computer-aided manufacturing of laminated engineering materials (CAM-LEM), where alumina or ceramics are the starting materials; selective deposition lamination (SDL), where standard paper sheets are used; composite based additive manufacturing (CBAM), where fabrics composed of long fibres fused with thermoplastic materials, carbon fibre combined with either Nylon 12 or polyether ether ketone (PEEK) and glass fibres with Nylon 12 and PEEK are used; and ultrasonic additive manufacturing (UAM), where variable material blends can be printed as long as they can be fused into a single object.

3.7 Directed Energy Deposition

Directed energy deposition (DED) refers to a group of processes that selectively employs a heat source to melt powders or metal wires simultaneously deposit them through a nozzle (Svetlizky et al. 2021; Gibson et al. 2015c). It is categorised into laser engineering net shape (LENS), where a laser beam is used to consolidate powders of metals, alloys, ceramics or composites; direct metal deposition (DMD), or laser deposition welding (LDW), where a nozzle is used to deposit metal powders; and electron beam additive manufacturing (EBAM), where an electron beam is used to deposit metal wires.

4 3D Printing for Tailored Therapy

At present, traditional mass production pathways entail the fabrication of medicines in a few, fixed doses, sizes and shapes (Awad et al. 2021c). Nonetheless, due to irregularity in inter- and intra-patient pharmacokinetic responses, therapeutic outcomes will vary (Madla et al. 2021). Consequently, not all medications are efficacious. As an example, oncology and Alzheimer's drugs are only efficient up to 25% and 30% of the cases, respectively (Gioumouxouzis et al. 2020). Besides, the lack in dose strength availability is particularly challenging for paediatric and geriatric patients due to their lower dosing requirements compared to standard adult patients (Breitkreutz and Boos 2007). Ordinarily, required dose strengths can be obtained by manipulating or crushing available pills, but this often culminates in errors and high dosing variability, leading to ineffective therapies or bringing about side effects of different severities and types (Habib et al. 2014; Madathilethu et al. 2018). Ergo, by offering these patient subgroups personalised treatments, therapeutic outcomes can be improved whilst reducing hospital admissions and incurred healthcare costs.

4.1 3D Printing of Medicines

In this regard, the use of 3D printing has been shown to be ideal for the fabrication of tailored 3D-printed dosage forms, termed Printlets™, combining the benefits of being a more reliable and reproducible production method (Awad et al. 2018a; El Aita et al. 2020). These dosage forms can be designed in discrete shapes and sizes, not only based on the individual patients' needs but also taking into account their preferences (Goyanes et al. 2017). As such, patients can be empowered to select their most preferable dosage form paired with the 3D printing technology that yields desirable properties (Januskaite et al. 2020), ensuring compliance to treatments. Patients have the choice between a wide array of dosage forms, ranging between capsules (Gupta et al. 2015; Pereira et al. 2020; Nober et al. 2019; Okwuosa et al. 2018) and tablets with different intake or release profiles (e.g. chewable (Tabriz et al. 2021; Tagami et al. 2021; Sjöholm et al. 2022; Chatzitaki et al. 2022; Rodríguez-Pombo et al. 2022b), orally disintegrating (Allahham et al. 2020; Eduardo and Ana 2021; Yi et al. 2023; Hu et al. 2023) or effervescent (Dong et al. 2022); instant (Fina et al. 2017; Jamróz et al. 2020), delayed (Okwuosa et al. 2017; Ou et al. 2023) or extended release (Gioumouxouzis et al. 2020)) all the way to suppositories (Chatzitaki et al. 2021; Awad et al. 2023a, b, c), films (Elbadawi et al. 2021; Elbl et al. 2020; Eleftheriadis et al. 2020) and pellets (Awad et al. 2019; Shpigel et al. 2018).

Whilst yet to be implemented, 3D printing could be employed to produce most medical products used in practice nowadays. This spans medicines (for human (Pyteraf et al. 2023) as well as animal use (Sjöholm et al. 2022)), medical devices, implants (Bassand et al. 2023; Xu et al. 2023), tissue engineering constructs and scaffolds (Guo et al. 2023; Ma et al. 2023). In comparison to traditional mass production processes, it has been indicated that 3D printing is more cost-efficient at producing small batches of bespoke objects (dos Santos et al. 2021). In fact, a major virtue of the technology is that production costs are not affected by the intricacy of objects being manufactured (Awad et al. 2018b). Additionally, modifications to an object's size and shape are executed using a computer-aided design (CAD) software, which is rapid and does not impart additional costs. To ensure printing accuracy and correct drug(s) concentrations, real-time quality control testing on the 3D-printed medications can be performed using spectroscopic systems (Edinger et al. 2019; Jørgensen et al. 2023). Alternatively, the 3D-printed drug products can be imprinted with quick response (QR) and data matrix (DM) codes, creating a safe and digital system for tracing and tracking them and ensuring their authenticity (Edinger et al. 2018; Trenfield et al. 2019; Öblom et al. 2020). In fact, this could extend the applications of 3D printing to tackle challenges such as opioid abuse (Ong et al. 2020; Nukala et al. 2019) and substandard and falsified medicines (Trenfield et al. 2019; Nørfeldt et al. 2019).

3D printing has been shown to be well suited for producing dosage forms with intricate configurations that are complex or impossible to create using traditional pharmaceutical manufacturing methods. As an example, the SLS and FDM

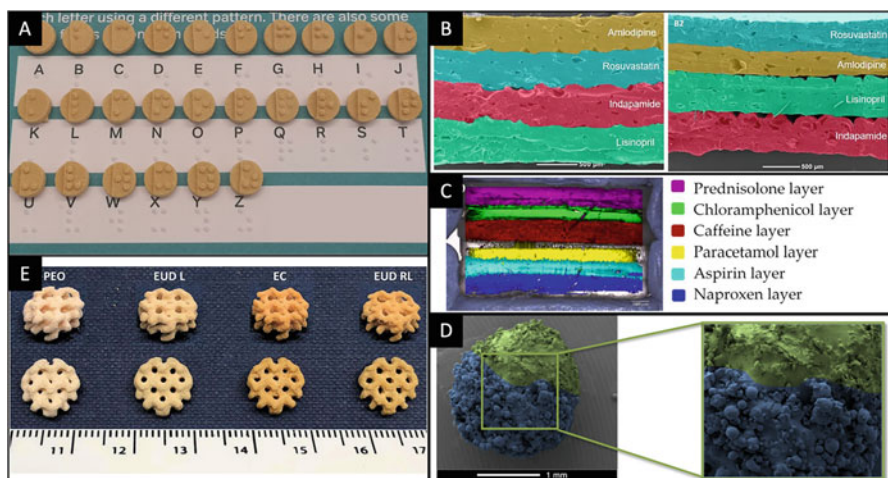


Fig. 1.1 (a) SLS Printlets with Braille alphabets on their surface (Awad et al. 2020b). (b) False-coloured cross-sectional scanning electron microscopy (SEM) images of a 4-layer polypill. Each individual drug layer is highlighted with a distinctive colour; lisinopril (yellow), amlodipine (orange), indapamide (green), and rosuvastatin (blue) (Pereira et al. 2019). (c) Raman mapping of an SLA 3D-printed polypill containing six different drugs showing the spatial separation of the layers (Robles-Martinez et al. 2019). (d) SEM image of a 2 mm SLS miniprintlet with dual drug regions. The green region represents the ibuprofen-ethyl cellulose region, whereas the blue region represents the paracetamol-Kollicoat Instant Release region (Awad et al. 2019). (e) SLS gyroid lattice Printlets made using different polymers, including (from left to right) polyethylene oxide, Eudragit® L100-55, ethyl cellulose and Eudragit® RL (Fina et al. 2018). Scale shown in cm. (Reprinted with permissions from their original sources)

technologies were employed to fabricate orodispersible Printlets with Braille and/or Moon scripts on their surface (Fig. 1.1a) (Awad et al. 2020b; Eleftheriadis and Fatouros 2021). This innovative approach provided a practical method for blind and visually impaired patients to identify their medications using tactile perception. In doing so, it can improve patients' independence and compliance to treatment, whilst reducing medication errors and hospitalisations. Similarly, 3D printing can be exploited as a modern strategy to fulfil the needs of patients on complex treatment regimes, such as those on a polypharmacy (i.e. the concurrent intake of five or more medications) preventing them from effectively managing their treatment (Wahlich et al. 2019). In this regard, several 3D printing technologies (i.e. SLA, SLS and FDM) were utilised for the production of multidrug-loaded dosage forms, termed 3D-printed polypills (or polyprintlets) (Fig. 1.1b) (Ghanizadeh Tabriz et al. 2021; Goyanes et al. 2015; Pereira et al. 2019). For instance, up to six different active pharmaceutical ingredients (APIs) can be incorporated into different multi-layered iterations, enabling the actives' release properties to be fine-tuned whilst reducing the number of medicine intakes from six to a single one per day (Fig. 1.1c) (Robles-Martinez et al. 2019). A similar concept can be applied to small dosage forms, such as 1 or 2 mm 3D-printed pellets (i.e. miniprintlets), where two different APIs can

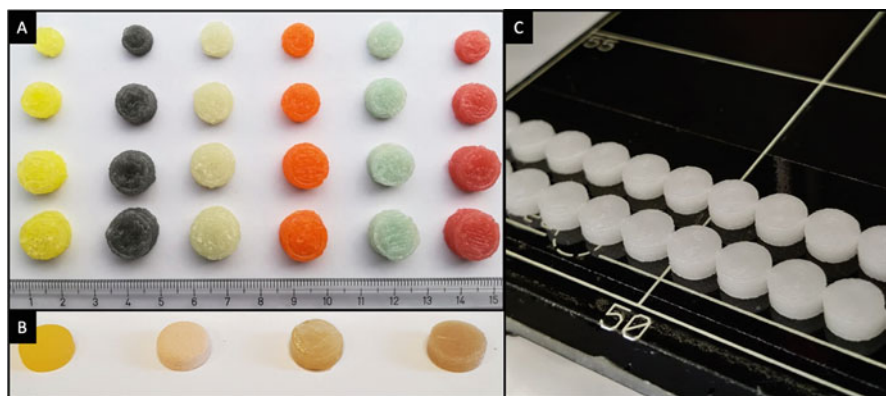


Fig. 1.2 (a) Chewable SSE isoleucine-loaded Printlets in different flavours-colours and doses: (from left to right) lemon-yellow, coconut-black, banana-light green, orange-orange, raspberry-light blue, strawberry-red and (from top to bottom) 50 mg, 100 mg, 150 mg and 200 mg (Goyanes et al. 2019b). (b) Placebo Printlets fabricated using four different 3D printing technologies (from left to right): DLP, SLS, SSE and FDM (Januskaite et al. 2020). (c) 3D-printed tablets containing 10 mg sildenafil (Lyousoufi et al. 2023). (Reprinted with permissions from their original sources)

have their own distinct release profiles within each single unit (Fig. 1.1d) (Awad et al. 2019). In a different approach, the drug release properties from 3D-printed dosage forms were fine-tuned by varying their internal and external layouts (Fig. 1.1e) (Pereira et al. 2019; Sadia et al. 2018; Isreb et al. 2019; Arafat et al. 2018; Fina et al. 2018).

To evaluate the feasibility of using 3D printing for personalised medication, a 3D printer was placed into a hospital pharmacy to fabricate on-demand treatments for children (3–16 years old) suffering from a severe metabolic disorder – maple syrup urine disease (MSUD) (Goyanes et al. 2019b). Patients with this disease must be regularly monitored, and their dietary amino acids (e.g. isoleucine) intake must be adjusted based on plasma levels. The use of SSE 3D printing facilitated the manufacturing of isoleucine-loaded Printlets that are both chewable and palatable (Fig. 1.2a). The Printlets were produced in an array of dose strengths, colours and flavours, wherein their ability to improve patient acceptability of treatment and in controlling the disease outcome was assessed. The Printlets were found to result in a better control over target blood concentrations of isoleucine when compared to the standard therapy using isoleucine powder filled in capsules. In addition, most flavours and colours tested were well accepted amongst the young patients, demonstrating the value of employing such a technology to treat special patient populations. In another study, children's (4–11 years old) visual perception of four 3D printing technologies (i.e. DLP, SLS, FDM and SSE) was evaluated (Fig. 1.2b) (Januskaite et al. 2020). Whilst the children initially preferred the DLP Printlets, interestingly, their preference shifted in support of the SSE technology once informed that the Printlets were chewable. More recently, the bioequivalence of a 3D-printed drug product prepared in a hospital setting was investigated (Lyousoufi

et al. 2023). The sildenafil citrate-loaded medicines (Fig. 1.2c) were developed and produced under Good Manufacturing Practice (GMP) requirements and tested for quality control. The 3D-printed tablets have been shown to have the required quality specifications. More importantly, clinical trials verified the bioequivalence of the 3D-printed tablets to the originator drug product, further advancing and supporting the use of 3D printing within pharmaceutical practice.

4.2 Patient-Specific Prosthetics, Implants and Medical Devices

Early uses of 3D printing within healthcare were mainly for the production of prostheses. Currently, it has been established as the gold standard for designing and creating personalised implants and prostheses for patients that need precise geometries and accurate fittings. Images obtained from medical scans (i.e. radiographs, magnetic resonance imaging (MRI) and computer tomography (CT)) are used to generate digital files and input specifications for cardiovascular and dental prostheses and limb replacements (partial or full) (Nagrath et al. 2018; Martin et al. 2021). One such example is the 3D-printed Osteoid™ medical casts which are tailored to individual users (Karasahin 2013). The use of 3D scans ensures secure and flawless fitting, whilst improving arm mobility. This is further supported by the lightweight structures resulting from low material infill, making the cast more comfortable for the wearer. The Osteoid technology also provides the added benefit of improved bone healing (i.e. up to 38% compared to standard plaster casts) and non-union fractures' healing (i.e. up to 80% compared to traditional methods) due to the use of ultrasound waves that pulsate for 20 min per day.

For custom-made drug-laden implants and medical devices, 3D printing is often paired with 3D scanner devices. This permits the design and fabrication of a multitude of devices for various applications, including nose masks for the treatment of acne (Goyanes et al. 2016), masks (Muwaffak et al. 2017) or scaffolds (Glover et al. 2022) for wound healing applications, mouthguards (Fig. 1.3a) (Liang et al. 2018) and antibiofilm multidrug-loaded hearing aids (Fig. 1.3b) for local treatments (Vivero-Lopez et al. 2021). Other types of bespoke drug-eluting 3D-printed devices include intravesical devices (Fig. 1.3c) (Xu et al. 2021b; Melocchi et al. 2019a; Rahman-Yildir et al. 2022), vaginal and intrauterine devices (Fig. 1.3d) (Salmoria et al. 2018; Tiboni et al. 2021; Maurizii et al. 2023; Utomo et al. 2023), intragastric devices (Melocchi et al. 2019b; Kong et al. 2019), punctal plugs (Fig. 1.3e) (Xu et al. 2021a), vascular grafts (Domínguez-Robles et al. 2021), ear implants (Haddow et al. 2022; Triacca et al. 2022), breast implants (Shi et al. 2020; Qiao et al. 2019; Yang et al. 2020) and subcutaneous devices (Economidou et al. 2019; Genina et al. 2016; Picco et al. 2023). In a different approach, it has been shown that tailored drug doses can be printed onto contact lenses for personalised medical interventions (Pollard et al. 2023).

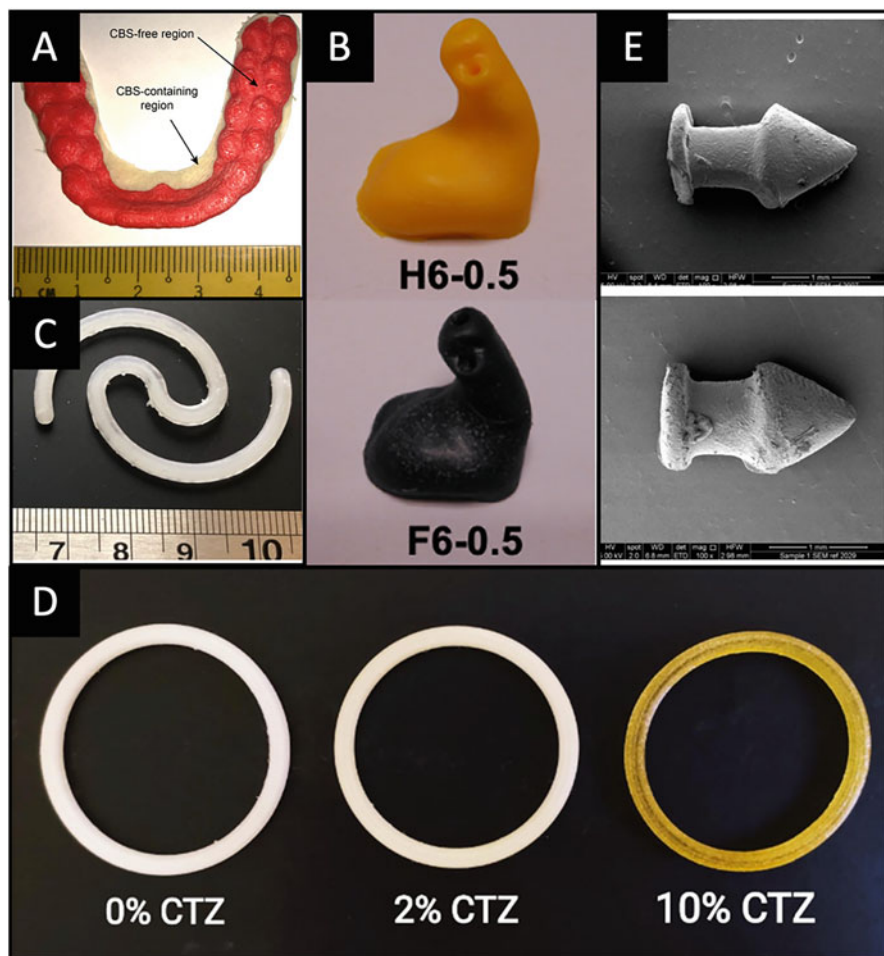


Fig. 1.3 Examples of different 3D-printed drug-laden implants: (a) a mouthguard (Liang et al. 2018), (b) hearing aid (Vivero-Lopez et al. 2021), (c) intravesical device (Xu et al. 2021b), (d) intrauterine device (Tiboni et al. 2021) and (e) punctal plug (Xu et al. 2021a). Scales shown in (a) and (c) are in cm. (Reprinted with permissions from their original sources)

4.3 Remote Medications

With the vision of therapeutic interventions becoming digital in the future, efforts have been made to allow for medications to be dispensed remotely (Trenfield et al. 2022; Awad et al. 2021a). Within the field of 3D printing, this has been shown to be possible using a compact, smartphone-enabled 3D printer (Fig. 1.4a) (Xu et al. 2021d). The concept is based on the use of a smartphone's screen to irradiate digital patterns onto drug-loaded liquid resins. This permits the on-demand printing of

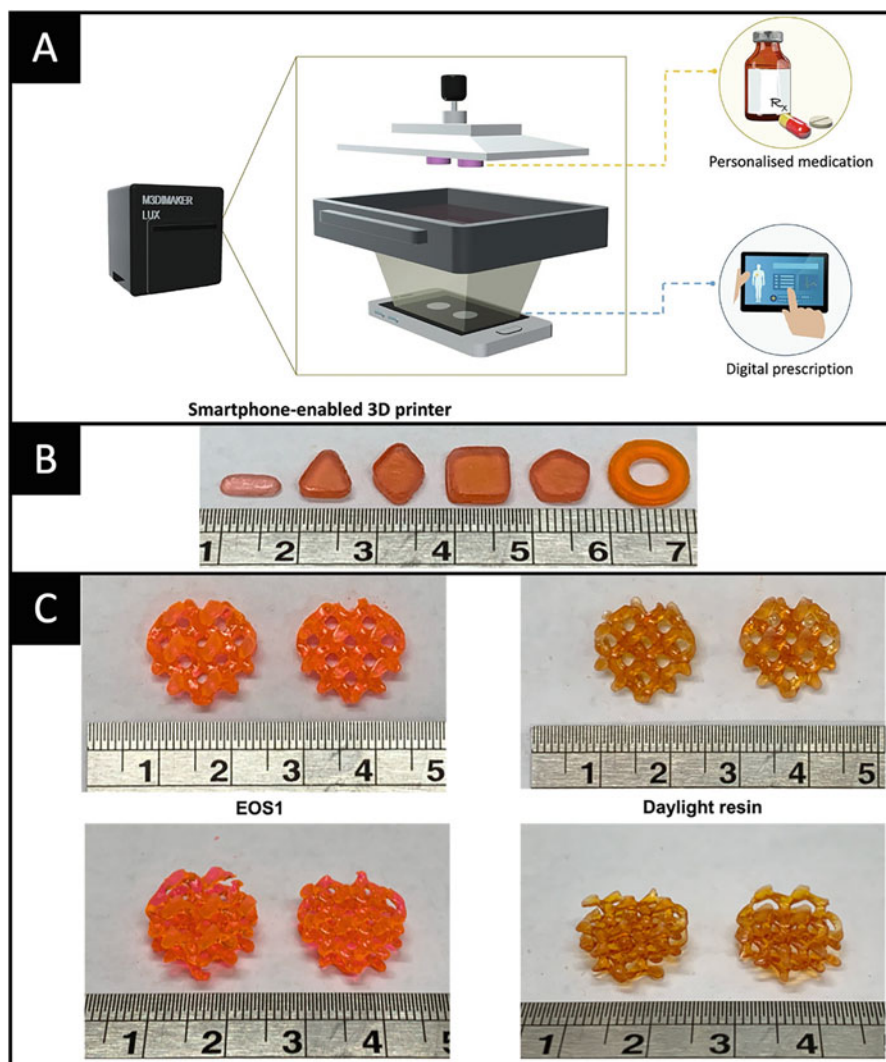


Fig. 1.4 (a) Graphical illustration of the smartphone-enabled 3D printing system. Photographs of (b) Printlets in various geometries including (from left to right) a caplet, triangle, diamond, square, pentagon and torus and (c) gyroid lattice Printlets prepared using this 3D printer. Scales shown in cm. (Reprinted with permission from Xu et al. 2021d)

patient-centric medications (Fig. 1.4b, c) at home, on the move or in the case of an emergency. With a custom mobile application in place, printing can be done in an easy and safe manner, where a healthcare professional overseeing the whole process. The proof-of-concept was established using warfarin sodium, an API with a narrow therapeutic index (Niese et al. 2019) and requiring a tight control over its dosing regimen to ensure an efficacious response and avoid potential toxicity (Vuddanda et al. 2018; Reynolds et al. 2007).

5 A Fourth Dimension

4D printing is a modern version of 3D printing where a fourth dimension, namely, time, is used to instigate a change in a static 3D-printed object using a stimulus (e.g. light, moisture, pH, electricity, magnetic field or temperature) (Kuang et al. 2019). Within pharmacy, this technology has been mainly applied to produce drug-loaded devices with retentive properties. For instance, expandable devices that can be retained within the stomach region were created using FDM 3D printing (Melocchi et al. 2019b). These devices are designed to assume a temporary form for ingestion after which they expand again to a size large enough to prevent their premature release from the stomach to the intestines. Thus, they are trapped there for extended periods of time, resulting in a constant local delivery of the drug in the stomach. This decreases the dosing frequency and improves therapeutic efficacy. A device based on similar principles was developed for the treatment of urinary tract infections (Melocchi et al. 2019a). Termed an intravesical retentive device, the FDM 3D-printed geometry was found to be capable of reverting to its original conformation swiftly but disintegrates within a few hours. An alternative method that involved the use of SLA 3D printing was used to fabricate another type of intravesical device (Xu et al. 2021b). Unlike its FDM analogue, the SLA device has shown to provide a constant lidocaine release over a period of 4–14 days, dependent on its internal infill material. In another approach, a bioinspired capsule was developed for controlled drug release based on temperature changes (Zu et al. 2022).

6 An Outlook of the Future of Medications

To support the integration of 3D printing within healthcare, it is anticipated that the technology can be combined with other ground-breaking cyber systems (Raijada et al. 2021), including artificial intelligence (AI) and machine learning (ML) (Abdalla et al. 2023; Ong et al. 2022; Mazur et al. 2023), computational modelling (Eleftheriadis et al. 2021), cloud computing and blockchain (Nørfeldt et al. 2019), remote diagnostic devices (Liu et al. 2021), robotics (Hann et al. 2020; De Marco et al. 2019), autonomous vehicles and drones (Trenfield et al. 2022; Awad et al. 2021a). By building interconnections between all these technologies, a modern healthcare model can be derived (Fig. 1.5). The envisioned framework is based on a multistage structure that includes diagnosis, prescribing, medicine production, dispensing and distant monitoring. Several different scenarios of how these technologies could be embedded together within healthcare have been suggested (Beer et al. 2021). One such example involves real-time patient data being remotely collected from wearable sensors and devices (e.g. smart watches and smartphones). A healthcare practitioner remotely accesses the data, assesses the patient's condition and issues a digital prescription. The latter is sent to a pharmacy or production facility where medications are fabricated on-demand to meet the individual patient's

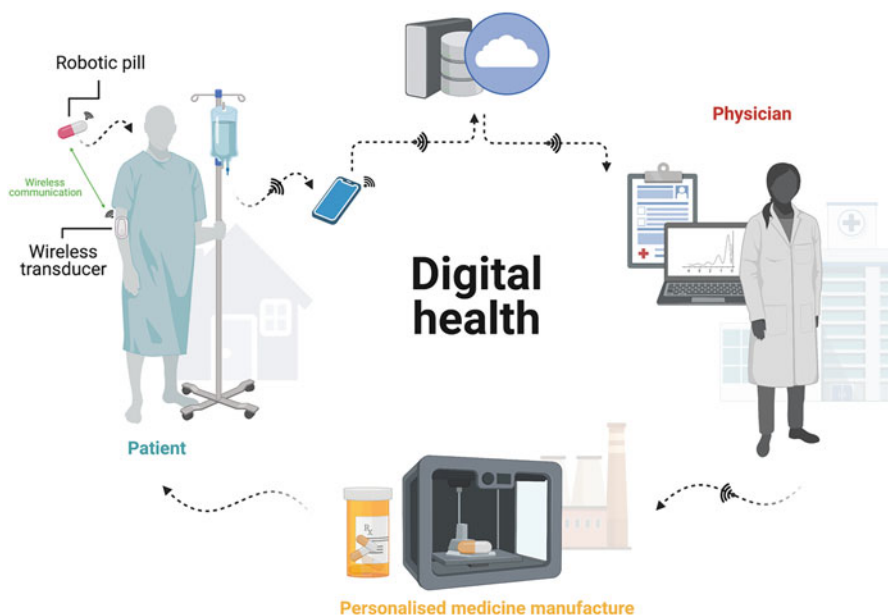


Fig. 1.5 Graphical illustration showing what a modern digital healthcare model might look like in the future. (Reproduced with permission from Awad et al. 2021a)

requirements. A robot then assists in packaging the medication and dispenses it to the patient by sending to his/her home using a drone. Lastly, the healthcare professional continues to remotely monitor the patient's progress and their compliance to the treatment plan. This cycle keeps repeating, delivering constant and bespoke medical care to patients at the comfort of their homes.

7 Conclusion

3D and 4D printing technologies have spurred great interest and gained substantial attention since their inception. Together with other digital health technologies, the printing systems open new avenues for creating safer and more effective medicines. With the additional dimension in 4D printing, these medicines can be made dynamic, allowing even more advanced control over the drug delivery properties and therapeutic response. With these technologies being limited by ones' imagination, their full potential is yet to be realised. In fact, with five-dimensional (5D) printing being right at the corner, the prospects of these technologies are becoming more enticing to look forward to.

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Chapter 2

3D Printing for Novel Dosage Form Design



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Abstract Development of 3D-printed dosage forms has expanded rapidly over the last few decades, and the potential for their use in clinical practice continues to grow. Through 3D printing (3DP), dosage forms with unique properties can be made that would be difficult to produce using conventional manufacturing. In addition to dosage forms for oral administration, 3DP is also an established method of creating implants, microneedles, and other formulations for drug delivery. The flexibility that 3DP provides allows for patient-specific features such as customising a combination of drugs with different strengths but also adjusting factors that depend on the drug itself such as controlled release for antiepileptics, or immediate release for analgesics. This chapter covers some of the recent advancements in solid oral dosage forms using 3DP, such as gastro-retentive floating tablets, polypills, complex geometric designs, and functional aesthetics. We also highlight the key features of these formulations and their implications in the clinic.

Keywords 3D printing · Dosage form design · Personalised medicine · Pharmaceuticals · Polymers · Drug development

1 Introduction

Advances in 3D printing (3DP) technologies have seen additive manufacturing become more accessible, reliable, and affordable. There are now countless examples of 3DP applications in the automotive, aerospace, and industrial sectors, where rapid prototyping is used to manufacture parts much faster than other methods while allowing for on-site production and less waste (AML3D 2022; Thomas and Mishra 2022). More recently, 3DP has taken a rapidly expanding role in the healthcare field, printing medical devices like orthodontic devices, orthotics, implants, and pharmaceuticals.

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3DP can create objects that are difficult and impractical to produce with conventional manufacturing methods such as direct compression and wet granulation. In the pharmaceutical field, this can present in the form of functional aesthetic features, complex geometric designs, floating tablets, and even polypills. Features like these are simple to implement and can tune many features of the printed tablet, also referred to as a printlet. Drug release kinetics can be changed by making a hollow tablet or by modifying the internal infill geometry, allowing for easy adjustments between immediate or sustained-release. The dose and number of active ingredients can be adjusted using polypills, and this can be combined together with aesthetic modifications such as adjusting the colour or shape of a tablet, which can aid patient compliance to complicated drug regimens.

Clinical integration of 3D-printed medications has already begun, and it seems likely that progress will continue steadily over time. In 2015, the first ever 3D-printed oral medication SPRITAM[®] was approved by the US Food and Drug Administration (FDA), containing an antiepileptic medication in an orodispersible dosage form (Jacob et al. 2014; U.S. Food and Drug Administration 2016). It dissolves in the mouth in only a few seconds, making it a perfect alternative for those who have trouble swallowing large tablets, as is common in paediatric and geriatric populations (Konta et al. 2017). These tablets are made using binder jetting (BJ), a 3DP process that allows for the creation of a highly porous and therefore rapidly dispersible tablet. This product, although manufactured by 3DP, is in a practical sense the same as its conventionally manufactured counterparts. This is because there is no potential for customisability in terms of dose, release profile, or other features like colour or flavour. Over 2021–2022, Triastek[®] received Investigational New Drug (IND) approval from the FDA for two new 3D-printed medications (TRIASTEK 2022), meaning that in the coming years, we may see additional 3D-printed drugs enter the market, perhaps even with options for customisation.

In the current pharmaceutical climate, the fact that features such as a tablet's appearance, dose, and active ingredients are fixed means that treatments can become generalised to the average patient instead of tailored to the individual. Part of the reason behind this is that conventional pharmaceuticals work on the principle of bulk manufacturing, meaning that only very commonly used formulations would be financially practical to make. Different people have different needs based on many factors such as sex, genetics, and age (Seyhan and Carini 2019), and therefore it is clear why the practice of empirical treatments can be detrimental to patient outcomes. Personalised medicine is evidently a key advantage of 3D-printed pharmaceuticals, but we are yet to see any approved products worldwide with the innovative customisability discussed in this chapter.

2 Unconventional Oral Dosage Form Design Using 3DP

The nature of 3DP allows for the creation of unique shapes, geometries, and therefore release profiles that would be difficult or impossible to achieve with conventional compression manufacturing. Several methods will be discussed that

directly change the delivery of a drug compared to a commercially available product, such as by using floating tablets or geometries to change release kinetics and polypills to deliver multiple drugs at customisable doses simultaneously (Khaled et al. 2014, 2015; Oladeji et al. 2022; Goyanes et al. 2015). Additionally, the aesthetics of a dosage form such as colour, shape, or flavour should not be overlooked, as it has the potential to benefit patients at high risk of medication-related harm (Awad et al. 2020). A paediatric patient may be more willing to take their medication if it is in their favourite colour or flavour, and some patients may benefit from embossing a tablet with symbols or braille to help recognition. There are many benefits of customisable medication over empirical regimens, and 3DP is proving to be a method of achieving personalised medicine in a way that conventional manufacturing cannot.

2.1 Improving Patient Adherence with Functional Aesthetics

It is well-known that the form that a given medication comes in, such as tablets, capsules, or orodispersible tablets, can affect patient compliance greatly (Alyami et al. 2017). Beyond simply the type of dosage forms, many other considerations exist including shape, size, colour, flavour, or texture. In current pharmaceutical manufacturing, medications have limited flexibility in terms of these options. A study of 331 adults surveyed responses to preferences of dosage form, shape, and size (Overgaard et al. 2001) and found that small, white, highly arched film-coated tablets were favoured by respondents the most often (Overgaard et al. 2001), but in reality this is not always a determinant of what conventional pharmaceuticals should or do look like. In some cases, a personalised dosage form may not just be a personal preference but a necessity, such as with dysphagia in the elderly, or excessively large tablets in paediatric populations. To remedy this, 3D-printed solid oral dosage forms could be used to customise a wide variety of aesthetic features, with the aim of keeping pharmacokinetic and pharmacodynamic properties consistent while simultaneously increasing adherence and keeping production costs reasonable. A summary of simple aesthetic modifications for 3DP applications is shown in Fig. 2.1.

Features like colour and flavour of a tablet are potentially some of the most impactful aesthetic modifications that can be made, yet are relatively easy to implement with 3DP. Several applications for this become immediately apparent, such as in the paediatric and geriatric populations or even simply for those with visual impairments like colour blindness. In the current pharmaceutical environment where the most common appearance of a tablet is small, round, and white, it can become increasingly difficult to recognise and distinguish different medications. Additionally, many generic brands of medications list only the drug name on the box, and understandably many patients with an average health literacy may not recognise what condition it is used to treat. Interestingly, it has also been shown that the colour of a tablet is linked to the patient's perception of its therapeutic benefit (Overgaard et al. 2001). Several types of 3DP, especially fused deposition modelling

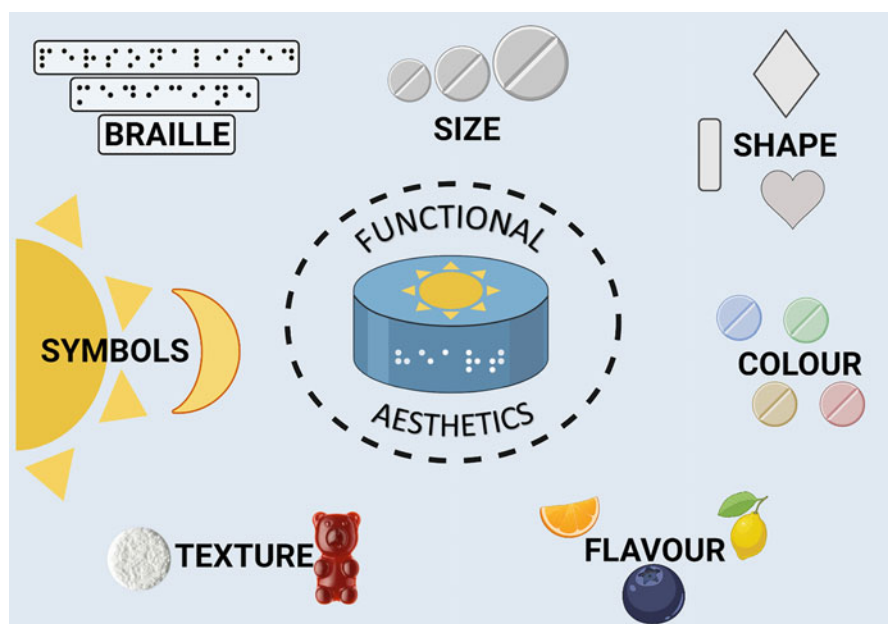


Fig. 2.1 Aesthetic modifications that can be made to solid or semisolid oral dosage forms using 3DP. Created with [biorender.com](https://www.biorender.com)

(FDM), pressure-assisted syringe (PAS), or selective laser sintering (SLS), can make tablets in a specified colour in a small batch by mixing a dye flavouring agent into the respective feedstock such as a paste or powder. In a paediatric setting, making a tablet into the patient's favourite colour or flavour could improve their adherence to a medication regimen. Several studies have assessed the feasibility and outcomes of these modifications to solid oral dosage forms (Goyanes et al. 2019; Januskaite et al. 2020). In a geriatric setting, or even within the general population, patients could choose which colours they want to represent which conditions, such as red for the heart. Additionally, patients could use custom colours to help them differentiate tablets that they are supposed to take every day such as blood pressure medication, from others including analgesics which may only be needed on a 'when required' basis. Similarly, braille and symbols can easily be added to a 3D-printed tablet (Awad et al. 2020). Braille could have significant benefit for those who are visually impaired, and symbols, similarly to a customisable colour, could help people recognise their medications. A useful example would be a sun or moon symbol to represent the time of day a medication should be taken. An interesting note about adding braille or a symbol to a 3D-printed tablet is that it would not require any modification to the formulation used to print the active pharmaceutical ingredient. Instead, a simple change in the 3D modelling software could allow for additions like these to be printed on top of the tablet, and compensate for the resulting increase in

tablet volume by modifying the dimensions of the tablet, or alternatively using an inert (drug-free) formulation for the braille.

Customising the shape and texture of 3D-printed solid oral dosage forms has also been investigated in several studies. As discussed, modifying the shape of a tablet can change the surface area to volume (SA:V) ratio and therefore the release kinetics, but the shape and texture of a medication can also be tuned to increase patient acceptance of medications. Modifying the shape of a printed object is simple, requiring no changes to the formulation, but rather importing the desired 3D shape into the printer's software. There are countless examples of modifying the shape of a drug-loaded tablet, especially for modifying release kinetics, but several studies have also assessed the effect of shape and texture on the patient acceptability of a medication, which importantly were applied in paediatric settings (Januskaite et al. 2020; Scoutaris et al. 2018). Patient surveys show as expected that different individuals have a preference toward a particular shape or colour, but interestingly a trend was observed that the majority of participants opted for a chewable tablet irrespective of the shape or colour of other tablets that had to be swallowed whole (Januskaite et al. 2020). In the current pharmaceutical environment, many medications necessary for paediatric use come in an oral liquid, or potentially only in a tablet that must be crushed and specially compounded into a liquid formulation. The paediatric population is especially prone to low acceptance and adherence to medications and being able to customise the delivery of a drug from a solid tablet or liquid into a chewable tablet could have pronounced benefits.

Achieving this specific level of customisability is not realistic with conventional pharmaceutical manufacturing. For example, even offering five different colours for a medication that comes in four different strengths immediately compounds to 20 unique products, let alone changing anything else like shape or size. Commercially this is simply not viable, but operating in small-scale manufacturing for customised dosage forms is where 3DP excels. Firstly, the type of printer used could easily determine the texture, such as FDM for solid tablets, SLS for orodispersible tablets, and PAS for gummies. Secondly, with any of these 3D printers, mixing in a food-grade dye or flavouring agent to the feedstock can easily change the colour and taste. Finally, with just the press of a button on the 3D printer's slicing software, braille or symbols can easily be added to the top of a tablet without the need for hardware changes. Every patient is bound to have their own preferences on the aesthetic appearance of a tablet and being able to create unique dosage forms for an individual patient on a small scale would be a significant clinical benefit of 3DP, filling a niche that cannot be addressed by conventional manufacturing. The effects of this level of customisability on patient health outcomes remains relatively unexplored, yet has substantial potential, and therefore conducting further research in this field will be critical for the future of pharmaceutical practices.

2.2 Geometric Designs to Modify Drug Release

Geometric modifications are another unique capability of 3DP, where shapes that would be impracticable or impossible to fabricate through conventional manufacturing can easily be printed. For example, conventional punch-and-die direct compression can generally only make solid tablets, but by simply modifying the infill density of a printed object through software, the overall density and even the SA:V ratio can be tuned (Khaled et al. 2018). This immediately opens two avenues for customisation: firstly, by keeping the tablet dimensions constant the infill density can be changed, directly changing the weight and therefore dose of a tablet; and secondly, the shape, infill density and infill pattern dictates the SA:V ratio of the tablet, such as by creating channels through the tablet allowing for an increased surface area available for drug diffusion. This can be augmented to meet different release profiles, such as the same formulation being either immediate or controlled release determined only by software-generated changes to geometry and density (Goyanes et al. 2015; Martinez et al. 2018).

As the size of a 3D object decreases or its infill density is reduced, the rate of drug release increases due to the resulting increase in SA:V ratio. One study compared the relationship between surface area, volume, and SA:V ratio and identified that different shapes can be produced at a constant volume or a constant surface area but consistently have different SA:V ratios (Goyanes et al. 2015). Following this concept, another study printed different shapes that naturally have different SA:V ratios, and although the changes of these ratios were somewhat minimal and drug release varied by only a few hours, it was also found that when the shapes were scaled to have a constant SA:V ratio, the release profile was near identical (Moldenhauer et al. 2021).

A torus shape, manufactured by stereolithography (SLA), has been identified in one study as the ideal candidate for SA:V ratio modification, achieving values between 0.5 and 1.0; a wider range than other shapes (Martinez et al. 2018). For higher SA:V ratios of up to 2.4, an object consisting of multiple tori linked together could successfully be printed (Martinez et al. 2018). Another study found that different shaped objects of a constant weight have SA:V ratios of 0.9 and 1.6 for a cylinder and torus, respectively (Vithani et al. 2019). In a hot-melt piezoelectric inkjet 3DP study, the tablet size was set between 0.2 and 1.83 mm, where a smaller tablet has a larger SA:V ratio (Kyobula et al. 2017). Using variable tablet sizes and infill geometries to create tablets with a constant weight or height resulted in SA:V ratios between 1.41–7.07 and 1.02–6.76, respectively, as shown in Fig. 2.2 (Kyobula et al. 2017). Another interesting observation is that as drug loading increases, even comparatively minor changes to SA:V ratios seem to influence the drug release rate significantly. A tablet of 81% drug loading made via PAS 3DP showed extreme variations of 12–70% release over 15 min, only by changing geometry and therefore SA:V ratio between values of 0.96 and 2.98 (Khaled et al. 2018).

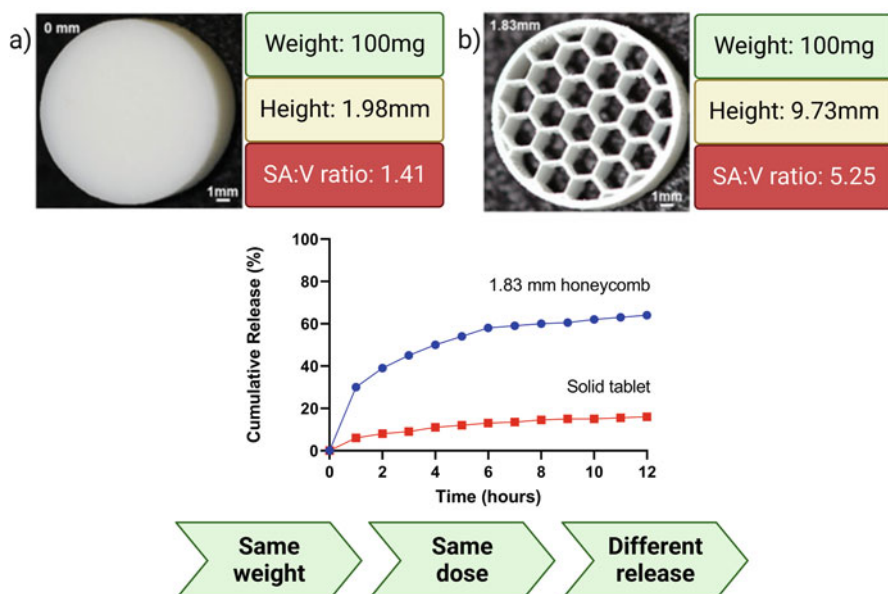


Fig. 2.2 The SA:V ratio and release rate comparison between (a) a solid tablet and (b) a tablet with honeycomb-shaped pores of 1.83 mm diameter. (Adapted from Journal of Controlled Release, 261, Kyobula et al., 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release, Copyright 2017, with permission from Elsevier)

Another method to increase the surface area or of a tablet is by creating pores. In itself, creating channels cross-sectionally through a tablet will increase surface area in the same way that decreasing the infill density does. Additionally, in the context of a shell/core model, pores can be designed to guide the dissolution media through the shell and into the inner drug reservoir, where drug release rate can be tuned by changing the characteristics of the pore (Shin et al. 2019; Fu et al. 2018; Jeong et al. 2020). The cross-sectional direction of the pore, as well as its length and diameter, also seem to play a role in modifying drug release. In a caplet-shaped model, having 9 pores that extended through the entire length of caplet led to a slightly slower release compared to 18 shorter pores that extended through the width of the caplet (Sadia et al. 2018a), a representation of which is shown in Fig. 2.3. This adds yet another point of modification for tuning drug release rates.

In a shell/core tablet structure, modifying the thickness of the shell or the density of the core allowed for release profiles ranging from 100% in 4 h to 80% over 10 h with controlled release kinetics (Zhang et al. 2017a). Similarly, a second study found faster release with lower infill density and additionally crafted accurate delayed and pulsatile-release profiles by adding drug-free shells in between drug-loaded segments (Lion et al. 2021). These examples display geometric changes not related to the size or density of the object but rather the physical location of the drug within the object.

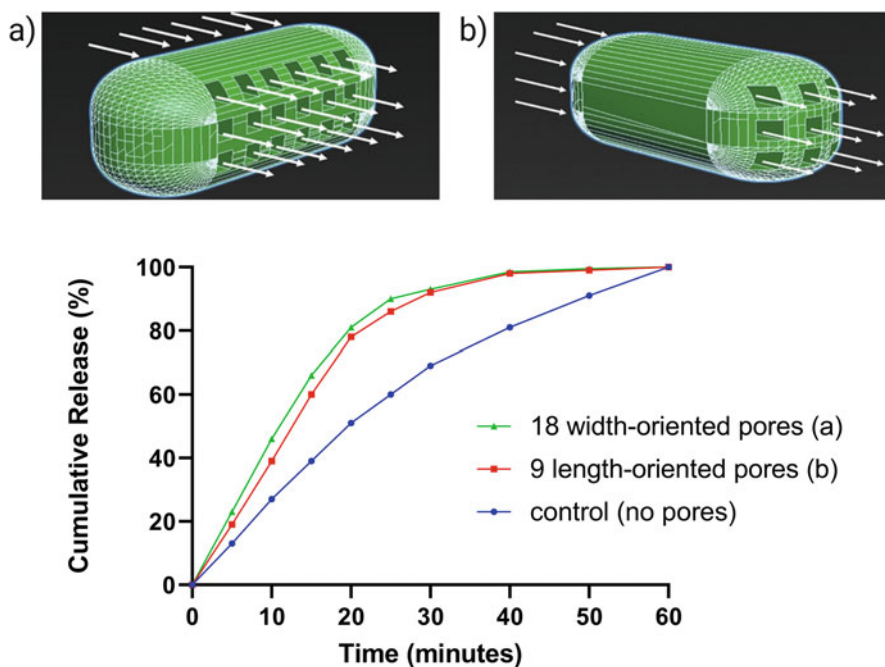


Fig. 2.3 Cross-sectional pores extending (a) along the width of the caplet and (b) along the length of the caplet. (Adapted from Journal of Controlled Release, 269, Sadia et al., Channelled tablets: An innovative approach to accelerating drug release from 3D-printed tablets, Copyright 2018, with permission from Elsevier)

In addition to creating different release profiles for a fixed drug dose, it is also possible to create a different drug dose with a fixed release profile. This can be done by changing the size of the tablet while keeping the SA:V ratio the same, maintaining a similar release profile at any drug dose, an important consideration in the context of dosing drugs with a narrow therapeutic window (Windolf et al. 2022a).

Further investigations into the relationship between SA:V ratio and release profile have shown evidence of some exceptions to this trend. One found that different shapes of a similar weight had only marginally different SA:V ratios (Goyanes et al. 2015). When the surface area was kept constant, the SA:V ratio dictated drug release rate, but when weight or SA:V ratio was kept constant, there appeared to be minimal variation (Goyanes et al. 2015). Another example involves the properties of swellable polymers such as Soluplus[®] (copolymer of PEG 6000, polyvinyl acetate (PVAc), and vinyl acetate (VA) in a ratio of 13:57:30). Soluplus[®] was observed to have no dependence on SA:V ratio but rather the level of material porosity that mediated drug release, similarly to other swellable systems (McDonagh et al. 2022). This is an important observation as many polymers used for pharmaceutical 3DP have swelling properties, such as hydroxypropyl methylcellulose (HPMC) or

polyvinyl alcohol (PVA) (Agubata et al. 2021), which in theory could close small pores as the infill density increases. Indeed, it has been found that high infill densities of 90% of Soluplus[®] seemed to deny free penetration of the dissolution media, and instead the object behaves more as a solid (McDonagh et al. 2022).

One of the most significant conclusions drawn from studies assessing geometry modifications is the development of a mathematical model capable of accurately predicting drug release over time (Windolf et al. 2021). After inputting the SA:V ratio, the predicted mean dissolution time (MDT) was compared against experimental values, where variations of roughly only 2% were observed (Windolf et al. 2021). The applicability of this formula was found to be consistent irrespective of drug solubility and between inert and erodible polymers (Windolf et al. 2021). If in future experiments, the mathematical model continues to show compatibility with many different drugs and polymers; there would be various indications for its use in practice. For example, drug release over time would not have to be experimentally determined with countless different possibilities of drug combinations in unique geometries, but could rather be mathematically predicted (Windolf et al. 2021). In theory, this could also be reverse-engineered to generate a geometry with a SA:V ratio tailored to the type of drug, such as a high value for an immediate-release analgesic or a low value for an extended-release antiepileptic.

2.3 *Gastro-Retentive Tablets*

The creative design approach of making a floating drug delivery system allows for gastric retention and localised drug release in the stomach or upper gastrointestinal tract (GIT), which has been successfully demonstrated by 3DP on several occasions. While conventional floating dosage forms do exist, they are often made by incorporating sodium bicarbonate, which releases gas and makes the tablet more porous and therefore less dense than the gastric fluid. With 3DP the addition of sodium bicarbonate is not necessary, and instead a tablet can simply be printed to incorporate an air pocket to enable floating, as shown in Fig. 2.4. Using these geometric designs to enable floating would be impractical or otherwise impossible to create via conventional manufacturing, and 3DP could capitalise on this niche. Floating dosage forms can be useful for achieving release over a longer timeframe, with consistent and predictable release over that time. The tablet is made to be less dense than the medium around it and therefore floats, while the drug diffuses out slowly.

Controlling the rate of drug release consistently over time is the goal of all controlled release formulations (Zhang et al. 2017b) and is especially relevant for drugs that are difficult to dose. With some medications, the gap between the serum level that gives a therapeutic effect and that which causes side effects is very narrow. Fluctuating serum levels may lead to regularly alternating between levels that are too low and too high, thereby spending less time within the therapeutic window and precipitating side effects. Examples of the clinical benefit of this include medications such as those used for Parkinson's disease, where dopamine supplementation is first-

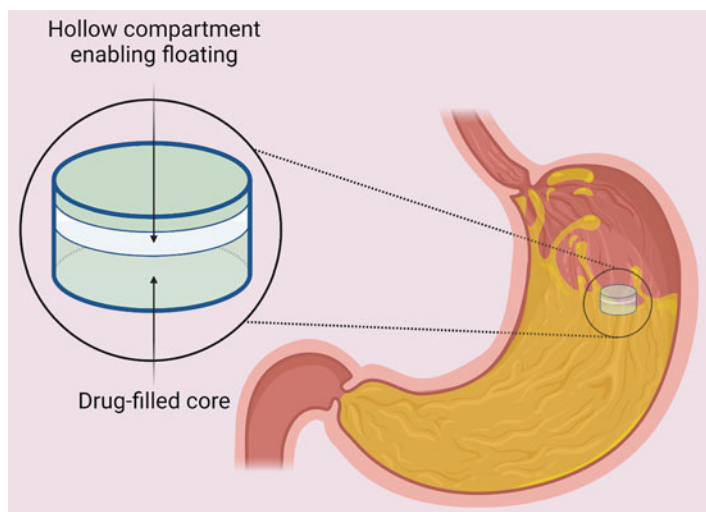


Fig. 2.4 Design of floating tablets using a hollow compartment structure via 3DP. Created with biorender.com

line treatment, but fluctuations of dopamine levels in the brain precipitate side effects such as reduced mobility (Windolf et al. 2022a). Similarly, it has been suggested that maintaining controlled release with antiepileptic drugs could reduce their side effects and better achieve therapeutic doses (Lim et al. 2016). If the dosage form can float on the surface of the gastric fluid, complications that compromise controlled release such as abnormally rapid gastric emptying may be minimised as the transit time in the GIT is increased. This is especially relevant for drugs that are absorbed in the upper small intestine or may face issues such as saturating transporters, whereby releasing a drug slowly amount over a longer timeframe could improve dosing efficiency, reduce dose frequency, and increase bioavailability. With the right material selection and tablet design, these floating tablets can be manipulated to have controlled release, and factors such as infill percentage and polymer solubility can change the profile from several hours to a few days.

A number of studies have used an FDM-printed polylactic acid (PLA) shell manufactured with pores or windows, as mentioned previously in geometric modifications, to allow for controlled dissolution of a conventional tablet inside (Shin et al. 2019; Fu et al. 2018; Jeong et al. 2020). However, having a shell printed in PLA could be problematic in practice as it is practically insoluble in hydrochloric acid and water (Heikkinen et al. 2018). An in vivo study of beagle dogs found that a PLA shell remained visible via X-ray imaging until 48 h after administration (Shin et al. 2019). Following this, it is not clear whether the PLA was dissolved or if the floating compartment of the shell was breached, causing the tablet to sink and pass through the GIT relatively intact. This could be a barrier to the application of PLA in oral dosage forms if its degradation in the GIT is not fully understood. Additionally, using direct compression for the drug-loaded core reduces the full potential of dose

customisation with 3DP. On the other hand, since the shell is 3D-printed, parameters such as the number of pores and their width could be changed, adjusting the release profile if desired.

To streamline this process into a single step, several studies have similarly used the shell/core design to allow for a floating tablet using polymers with greater water solubility, still using FDM technology. For example, using Soluplus[®] as the main polymer enabled 11 h float time, and a hydroxypropyl cellulose (HPC) hybrid blend floated for 12 h (Oladeji et al. 2022). There are many examples that follow this same principle, and there appear to be many different compatible polymers. HPC on its own or hybridised with other polymers has been used on several occasions for floating tablets (Chai et al. 2017; Reddy Dumpa et al. 2020; Vo et al. 2020; Giri et al. 2020). HPMC (Fang et al. 2022; Qian et al. 2022; Zhao et al. 2022) and HPMC acetate succinate (HPMCAS) (Lamichhane et al. 2019) have also been successfully used. Finally, PVA, being one of the most popular pharmaceutical-grade FDM-printable polymers, is also a common choice (Windolf et al. 2022a; Charoenying et al. 2020a, b, 2021; Chen et al. 2019). PAS has also been used, taking advantage of the gelation properties of certain polymers upon contact with an aqueous medium (Falcone et al. 2021, 2022), or by using an alcohol-based solvent which evaporates after printing, leaving the resulting tablet with a high porosity and low density (Chen et al. 2021; Li et al. 2018, 2019; Lin et al. 2021). There are many examples in practice where frequent dosing is required, and floating drug delivery could mean taking doses less often, reducing the pill burden of the patient and potentially improving adherence to medication regimens.

3 Polypills

One of the most innovative and advantageous applications of 3D-printed pharmaceuticals is creating what are generally referred to as polypills, a combination of multiple drugs in the same tablet. Although combination tablets exist on the market today, the combinations of drugs and their respective doses are pre-set, and personalising them is not an option. Some of the most common printing technologies, including FDM, PAS, SLA, and SLS, have been utilised to successfully manufacture polypills, ranging from two to six active ingredients per tablet.

One of the simplest ways to make a polypill is to use FDM 3DP to manufacture a drug-free multicompartiment shell, which can then be filled in a separate process with the chosen drugs, as represented in Fig. 2.5. This process has been used with a filament of Eudragit L100-55, a polymer with pH-dependent release (Keikhosravi et al. 2020). This was used to make a tablet with two compartments, into which aspirin and simvastatin-loaded solutions were injected, followed by printing a cap on top of this shell (Keikhosravi et al. 2020). This design shows customisability in that different shells with different compartments could be printed if desired, and in theory any drug-loaded liquid could be injected. The concentrations of the drugs used in this study were not at clinically relevant doses, but nevertheless this serves as a valid

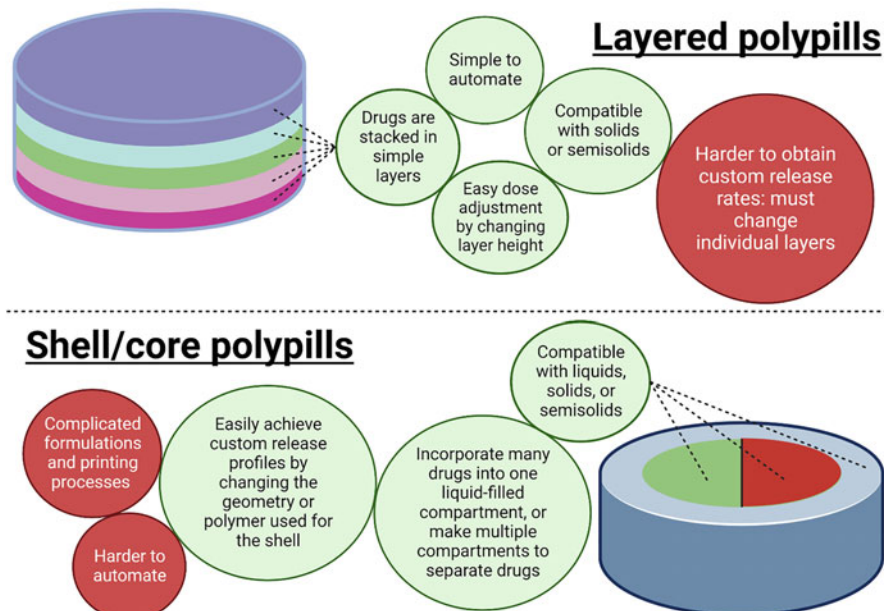


Fig. 2.5 Visual representation of two unique types of polypills able to be manufactured using FDM 3D printing. Created with biorender.com

proof-of-concept. Several similar studies have also been conducted under the concept of a printed shell manually filled with a drug-loaded liquid, including a self-microemulsifying drug delivery system (SMEDDS) for enhanced delivery of up to six poorly water-soluble drugs (Barber et al. 2021), or with four unique drug-loaded hot-fill fluid formulations (Pereira et al. 2020). The drawback of this type of design is that the process is not automated; the operation is paused after printing the shell, and then the liquid is manually injected, before resuming the print to finish the tablet. This is therefore a more complex and time-consuming process than standard FDM printing and additionally creates more situations where human error can take place.

The problem of manual intervention during the printing process has been overcome in a different study, where an FDM-printed shell was filled with liquid by an automated dispenser (Okwuosa et al. 2018). Another solution to this is simply changing the formulation to be compatible with filaments made by HME, whereby a shell/core geometry can be simultaneously printed via a dual-extrusion FDM system. On the other hand, using drug-loaded filaments may not be possible in some circumstances, such as with a SMEDDS formulation, where the benefits of enhanced drug delivery may outweigh the drawbacks of a more complicated manufacturing process.

The sequential processes of HME/FDM have also been used to load drugs either into separate filaments for layered coextrusion or into the same filament for printing several drugs in one step. One example utilising a Eudragit E PO-based filament has

been used to print two drugs in consecutive layers (Sadia et al. 2018b). A unique study also used an ethyl vinyl acetate (EVA)-based filament loaded with two drugs, layered with a PVA-based filament containing a third drug (Windolf et al. 2022b). An example of both options has been demonstrated by combining four drugs into four separate filaments or conversely blended into the same filament (Pereira et al. 2019). This study identified unique complications to layering drugs and found that placing a poorly soluble drug in the middle of a standard cylindrical tablet inhibited its release significantly, as it has much lower surface area for dissolution compared to the drugs placed on each end of the disc (Pereira et al. 2019). A drawback of the following experiment in this study, combining the four active ingredients into a single filament, is that the doses of an individual drug cannot be modified without also changing the others. This process is faster and simpler than layering four separate filaments consecutively and may be ideal for use with drugs with a dose that rarely changes, but in many cases the ability to titrate drugs individually would be more valuable.

PAS has also been used on multiple occasions to manufacture polypills in shell/core, multicompartment, and layered structures, just as with FDM. One study used a shell/core structure and interestingly found that increasing the amount of drug in the shell enhanced the release of drug in the core by disrupting the structure of the viscous and swellable matrix-forming polymer HPMC in the shell (Alayoubi et al. 2022). Another example includes an immediate-release paste containing several B vitamins, encasing a sustained-release core loaded with caffeine (Goh et al. 2021). Currently, the highest number of drugs in a polypill produced by PAS is five, which had different compartments for sustained or immediate-release (Khaled et al. 2015). A similar study incorporated three drugs into two compartments, but beyond simply tuning the release to be sustained or immediate, one compartment was designed to exhibit an immediate release profile, while the other was controlled release (Khaled et al. 2015). For more precise tuning of release profiles, another study has used drug-free and drug-loaded inks and simply changed the geometry of tablet design to switch between pulsatile, delayed, and continuous release (Haring et al. 2018).

Although the extrusion-based technologies of FDM and PAS are the most common choices for polypills, there are also examples of SLA, SLS, and BJ. Currently, SLS has been used on one occasion to print a polypill with two drugs (Trenfield et al. 2020). However, similarly to the FDM studies where several drugs were incorporated into the same filament, here the two drugs were in the same powder formulation and printed together, and thus individual dose titration of one drug would not be possible without changing the whole formulation. SLA has been used to print up to six drugs in one tablet, where once again the geometry of the tablet was also modified to create different release profiles (Robles-Martinez et al. 2019). At a specified point in the printing process, the print was paused, and the resin was swapped to one containing a different drug, and the print was then resumed (Robles-Martinez et al. 2019). Another SLA study printed four drugs, including amlodipine, which interestingly was found to have an interaction with the main matrix-forming polymer, severely inhibiting its release (Xu et al. 2020). One study has used BJ 3DP for polypills; however, the shell of the capsule produced via BJ was

drug-free, and instead each compartment of the capsule was filled with a different drug-loaded ink before the two pieces were joined together (Acosta-Vélez et al. 2018).

3DP polypills have the inherent advantage over conventionally manufactured counterparts in that custom drugs can be combined at custom doses, tailored to the individual who is being treated. Beyond this, the method of 3DP means that simple adjustments like infill density, polymer choice, and even geometry can customise release profiles and ultimately change the delivery of the drug. Tuneable parameters like these increase the flexibility of this type of dosage form design, but this will present its own challenges such as drug interactions, the risk of which may increase as more drugs and materials are found to be compatible with 3DP. Nevertheless, it seems clear that the benefits of manufacturing personalised polypills far outweigh these drawbacks. A small pilot study interviewed patients on the topic of 3D-printed medications, where the concept of 3DP polypills was a topic (Fastø et al. 2019). The general response from the interviewees was the polypills were exciting, due to reducing the number of tablets consumed daily for those with a large tablet burden (Fastø et al. 2019). However, limitations were brought up such as the inflexibility for dose changes, which was believed to increase the risk of errors involved in manufacturing (Fastø et al. 2019). Additionally, the opinions of doctors and pharmacists relating to the prescribing of 3D-printed dosage forms, including polypills, have been gathered. It was found that the majority of respondents had positive feedback about the benefits of 3DP tablets, and 60% were willing to prescribe them (Fastø et al. 2019). The three most apparent points of concern regarded formulation, manufacturing, and administration. Importantly, 98% of respondents agreed that 3DP polypills will improve patient adherence, particularly in those with polypharmacy (Fastø et al. 2019). It would be interesting to revisit these topics with patients and health professionals with a discussion or education session regarding on-site manufacturing, so that dose changes or switching drugs entirely could be managed in an instant, as opposed to in a conventional bulk-manufacturing setting where this would understandably be a concern that is difficult and time-consuming to address. The application of 3D polypills in practice would undoubtedly cause significant disruption to the current pharmaceutical polypill environment, which is severely lacking not only in the number of drug combinations available, but their doses as well.

4 Conclusion

3DP opens avenues for creating dosage forms that would be difficult or very impractical to manufacture with conventional methods. Adapting 3DP to an individual drug such as by changing the release profile can be achieved as easily as by changing the polymer used to deliver it or simply by using geometry or shape to change the SA:V ratio. The release profile can be tailored to what suits the drug, for example by its therapeutic window. Most importantly, pharmaceutical 3DP is

intended to be tailored to the individual patient, aiming for personalised medicine rather than an empirical ‘one size fits all’ approach. This chapter has covered many ways where patient health outcomes could be improved, for example, through increased adherence due to helpful aesthetic features or polypills. Additionally, the tailored release profiles for the drug could also help patients especially in terms of reducing side effects. Controlled release kinetics could be used for drugs that need very stable serum levels, or even pulsatile release for drugs like levodopa which conventionally require very frequent dosing to avoid serious side effects. Rapidly advancing progress in literature, clinical trials, and FDA approvals indicates that clinical integration is well underway, but it remains to be seen whether the avenues of customisability that 3DP brings will be put into practice.

MCQs

1. Which one of these factors will NOT influence surface to volume (SA:V) ratio of a tablet?
 - (a) Size
 - (b) **Polymer choice**
 - (c) Shape
 - (d) Infill density
2. Which of the following aesthetic features could aid patient adherence?
 - (a) Colour
 - (b) Visual aids such as braille
 - (c) Flavour
 - (d) **All of the above**
3. Which of the following is a drawback of fused deposition modelling (FDM) 3D printing?
 - (a) Few compatible polymers
 - (b) **Challenging to process thermolabile drugs**
 - (c) Minimal potential for scalability
 - (d) Requires larger warehouses than conventional tableting
4. What is the major limitation of the most commonly used 3D printing material, polylactic acid (PLA), in oral dosage forms?
 - (a) It is not biocompatible
 - (b) It has interactions with many drugs
 - (c) **It has poor solubility in water**
 - (d) It is not biodegradable
5. Which one of the following statements about SPRITAM[®] is INCORRECT?
 - (a) It was the first 3D-printed oral dosage form approved by USFDA in 2015
 - (b) **The tablets were made using customised Fused Deposition Modelling process**

- (c) These tablets were made using Binder Jetting 3DP process
 - (d) It is an orodispersible tablet designed to dissolve in mouth in few seconds
6. TRUE or **FALSE**: As the size or infill density of a 3D object decreases, the rate of release also decreases.
7. Which of the following model design approaches would most likely result in an extended-release profile?
- (a) Including hollow channels through the tablet
 - (b) Reducing the infill density of the tablet
 - (c) **Including a hollow chamber to allow the tablet to float**
 - (d) Choosing a tablet shape with a high SA:V ratio
8. The term ‘polypills’ refers to:
- (a) Multiple polymers being combined in a single formulation
 - (b) 3D printing multiple dose forms in a single print run
 - (c) 3D printing polylactic acid (PLA) based dose forms
 - (d) **Multiple drugs being combined in a single dose form**

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Chapter 3

3D Printing and Regulatory Considerations



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Abstract The healthcare industry in general and the pharmaceutical industry in particular are advancing at a rapid pace. As the world continues to advance, patients and families are becoming more aware of the customisation options available to them (Klein GT, Lu Y, Wang MY, *World Neurosurg* 80:233–235, 2013). The introduction of novel delivery methods of drugs and other pharmaceutical products, in line with the addressing the personalised requirements of every patient, is the need of the hour (Gross BC, Erkal JL, Lockwood SY, Chen C, Spence DM, *Anal Chem* 86:3240–3253, 2014). Additive manufacturing or 3D printing, as it is commonly known, satisfies this need and provides a strong solution for customisation. This chapter provides insight into the different types of 3D printing processes used in the industry, the need for quality control and good manufacturing practices, and eventually discusses the risks associated with 3D printed pharmaceuticals to patients. With an understanding of these aspects, this chapter lists the different approval departments that exist, explains how 3D printing can be regulated and discusses the proposed framework of 3D printing medical devices by CDRH, FDA.

Keywords Regulatory · Quality control · Good manufacturing practise · Medical devices · Risk · Regulatory agency

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1 Global Perspective of 3D Printing in Pharmaceutical Industry

The healthcare industry in general and the pharmaceutical industry in particular are advancing at a rapid pace. As the world continues to advance, patients and families are becoming more aware of the customisation options available to them (Klein et al. 2013). The introduction of novel delivery methods of drugs and other pharmaceutical products, in line with the addressing the personalised requirements of every patient, is the need of the hour (Gross et al. 2014). Additive manufacturing or 3D printing as it is commonly known satisfies this need and provides a strong solution for customisation. It offers healthcare providers the opportunity to alter the composition, dosage, rate of delivery, and other pertinent parameters pertaining to the drug at the most minute levels (Klein et al. 2013; Gross et al. 2014).

Simply put, the growth of 3D printing and its increased adoption in the pharmaceutical and healthcare sector have the immense potential to disrupt the dosage, supply chain, and waste management of conventional drugs (Chia and Wu 2015; Liaw and Guvendiren 2017). This, in turn address some pressing issues pertaining to on-demand manufacturing, feasibility, improved size and profile, dosage and geometry, and enhanced bioavailability with desired drug release profiles providing minimal toxicity or adverse drug reaction issues (Varghese et al. 2022).

The advantages of this customisation are particularly useful in the case of paediatric and geriatric patients, who may need to take a modified dose in tune with their age and body weight. Similarly, visually impaired patients would also need customisation to identify drugs based on their profile, rather than by reading text (Giannopoulos et al. 2016; Schubert et al. 2014; Ashish et al. 2019; Basit and Trenfield 2022). When 3D printing is merely used to modify the profile to enable easy identification, it doesn't hamper the efficacy of the drug. Therefore, conventional drugs with simple cosmetic modifications may not need to be regulated. However, when the profile of the drug is modified to increase the rate of absorption or improve bioavailability, it may change the overall efficacy of the drug for the better or the worse. Therefore, in such scenarios it is important that the 3D-printed drug be regulated to improve and ensure patient safety.

The global perspective on regulations pertaining to the pharma industry is that there are plenty. When it comes to biological materials however, such as 3D-printed grafts and implants, creating a regulation is quite convoluted, with the ethical considerations that need to be considered in such situations playing a major role (Klein et al. 2013; Varghese et al. 2022; Schubert et al. 2014).

Ultimately, across the world people are striving hard to make precision medicine a reality. 3D printing is one of the cornerstones of precision medicine for it has the power to personalise a significant aspect of healthcare. Likewise, 3D printers designed to print drugs alone are currently being designed. Therefore, the possibilities are immense, and regulating 3D printing to ensure quality healthcare is the need of the hour. To get there, we shall first briefly understand the different types of 3D-printing processes (which will be covered in detail in later chapters) and then

move on to understand how quality control and good manufacturing practices (GMP) can help manufacture these drugs. Next, we highlight possible risks of 3D printing drugs, pharmaceuticals, and implants. Having understood the processes, the quality control expected, and the risks, we discuss the regulatory considerations and close this chapter with what the future could possibly hold in this field of work.

2 Types of 3D-Printing Processes

3D printing has been in existence for the past couple of decades and has been used in the production of a variety of objects right from toys to weapons and space components. It comes under the umbrella of additive manufacturing, which is the fabrication of objects by layer-by-layer deposition. The models are designed through computer-aided design (CAD) and then fed to the system as a stereolithography (.stl) file. The model is then sliced into triangular segments, which constitute the layers that are to be printed. The introduction of this method has enabled parts to be manufactured faster, with more accuracy and resolution, and provides for more customisation through minor modifications in the composition of materials (Wong and Hernandez 2012; Souto et al. 2019).

The term 3D printing was first coined by the Massachusetts Institute of Technology (MIT) in 1993 (Sachs et al. 1993), which was filed for a powder-based technology to produce 3D objects. But the concept was in existence much before that when Charles Hull introduced a laser-based system for the creation of an '.stl' file in 1985 (Hull 1986). However, he did not use the term '3D printing' at that time. Since its introduction, the technology has been used in various fields. The applications of 3D printing include but are not limited to the manufacture of toys (Petersen et al. 2017; Brooks et al. 2014; Thierer and Marcus 2016), weapons (Thierer and Marcus 2016), aerospace components (MacDonald and Wicker 2016), etc. It is also widely used in the pharmaceutical industry for the making of implants (Popov et al. 2018; Nadagouda et al. 2020; Aimar et al. 2019), oral solid dosage forms (SODFs) (Gioumouxouzis et al. 2017; Okafor-Muo et al. 2020), stents (Khalaj et al. 2021; Cheng et al. 2017; Cabrera et al. 2017), bone substitutes (Popov et al. 2018; Cheng et al. 2021), lenses (Chen et al. 2018; Ali et al. 2021), and even finds its application in tissue engineering (Basit and Gaisford 2018). However, the main components used here are carbon and carbon-based materials as shown in Table 3.1, which pose several threats (Min et al. 2021).

3D-printing processes can be classified into several classifications. In this chapter, we will give a brief introduction on material extrusion, vat photopolymerisation, material jetting, binder jetting, and powder bed fusion.

Table 3.1 Pharmaceutical applications of materials

Material	Applications
Carbon	Heart valves
Ultrahigh-molecular-weight polyethylene (UHMWPE)	Bearing surfaces
Polyether ether ketone (PEEK)	Spinal cages
Polymethyl methacrylate (PMMA)	Bone cement, intraocular lenses
Silicones	Soft tissue augmentation, insulating leads, ophthalmological devices
Polyurethane (PU)	Pacemaker lead insulation
Expanded polytetrafluoroethylene (E-PTFE)	Vascular grafts, heart valves
Polyester textile	Vascular grafts, heart valves
Poly (styrene-block-isobutylene-block-styrene)	Drug eluting stent coating
Stainless steel	Stents, orthopaedic implants
Alumina	Bearing surfaces
Calcium phosphates	Bioactive surfaces, bone substitutes
Nitinol	Shape memory applications
Platinum group alloys	Electrodes
Cobalt-chromium alloys	Bearing surfaces, heart valves, stents, pacemaker leads
Titanium alloys	Dental implants, femoral stems, pacemaker cans, heart valves, fracture plates, spinal cages

2.1 Material Extrusion

Extrusion-based printing systems are the most commonly used systems due to their versatility and simplicity. The material used for fabrication is kept in a semisolid state and ejected through a nozzle. The ejected material is used to build layers derived from the slicing of the '.stl' file, and thus the final object is built through bottom-up construction. These systems can be classified based on the method used to liquefy the material as pressure-assisted microsyringes (PAM) (melting – reducing the temperature by increasing pressure) and fused filament fabrication (FFF) (melting – exposure to high temperature).

- *Pressure-Assisted Microsyringes:* Air piston is used as an extrusion channel for semisolid materials at a pressure of 3–5 bars, which causes a drop in temperature and thus conversion of the material into a molten state. After full construction of the object, solidification occurs only upon light exposure or drying. However, this kind of process poses the risk of deformation, excessive droplet shrinkage, or even collapse of the structure if it does not harden enough between each layer deposition. This technique also exhibits a low resolution as large orifices (0.4–0.8 mm) are used. Additionally, since it is a continuous flow process, a need for solvents arises to promote layer-layer addition and eradicate the aforementioned issues. But these solvents are often toxic and affect active

pharmaceutical ingredient's (API) stability during the fabrication or drying. The advantages of this method include the ability to be performed at room temperature, and it is highly suitable for making multidrug SODFs. It is also extensively used in tissue engineering.

- *Fused Filament Fabrication*: This method, also known as fused deposition modelling, is mainly used for the manufacture of SODFs by layer-by-layer deposition and hence its nomenclature. The main difference between PAM and FFF is that the thermoplastic raw material used here exists in the solid state, which is driven into the print head, after melting or softening by exposure to high temperatures, by a gear system. This causes the material to solidify instantly upon deposition due to a sudden reduction in environmental temperature, thus eliminating the risk of deflection and lack of solidification seen in the previous method. However, this also produces complexity in the process, as making solid filaments would require preprocessing steps like cutting, polymerisation, etc. Thermal heating also reduces the range of drugs that can be manufactured, as some polymers become unstable at high temperatures (Azad et al. 2020; Aguilar-de-Leyva et al. 2020).

The knowledge of the above methods shows that extrusion-based 3D printing has a wide range of applications in the pharmaceutical industry. Especially, they can be used in the bottom-up construction of single and multidrug dosage forms. However, this method entails some disadvantages. The printing accuracy is less (about 100 μm) in comparison to other methods like material and binder jetting (Duan et al. 2013). The material selection process for the ink is also complex, as the selected material must be reducible to gel form (gelation), should be able to withstand curing without deformation and should possess malleable properties. Additionally, due to the high shear force at the nozzle during extrusion, there will be microstructural defects in the material, which are inevitable. This might impact the ultimate strength of the product, as a cumulative addition of defects in each layer occurs (Gu et al. 2020). This poses a major health hazard, especially in the case of stents whose structural failure may have adverse health effects and may even cause the death of the individual.

2.2 Vat Photopolymerisation

As the name suggests, this process uses light to cure the photocurable resin. Generally, laser sources are used for this purpose to get a concentrated beam. Vat photopolymerisation is mainly used for the manufacture of complex structured metamaterials (Xu et al. 2021a), bone tissue engineering (Bahati et al. 2023), dentistry (Santos et al. 2022), SODFs, hearing aids, microneedles, and other medical devices (Xu et al. 2021b). Based on the arrangement of source, sensors, and resin, this method can be divided into four types, namely, line-wise scanning STL (SLA), mask projection STL (MPSL), microstereolithography (μSL) and two-photon polymerisation (TPP).

- **Line-Wise Scanning:** A top-down approach in which the configuration is like that of a typical commercial SL machine. In this method, each layer is irradiated line by line. It is mainly used in the manufacture of dental composites (used as fillers), which are highly viscous in nature.
- **Mask Projection:** This follows a typical 3D-printing bottom-up approach, where layers of material are irradiated one at a time. It is mainly used in tissue engineering, dental retainers, and the manufacture of SODFs.
- **Micro Stereolithography:** This is a method currently in incubation, where finer-resolution objects are manufactured, using high-frequency lasers for printing.
- **Two-Photon Polymerisation:** It is a variant of traditional laser-based stereolithography, but the polymerisation is done by the simultaneous absorption of two photons, rather than one, by the resin surface. This method is also used to obtain objects with very fine resolution; thus, minute features can be obtained. It is mainly used in the manufacture of stents and SODFs (Zhang et al. 2021).

Though the accuracy and resolution of this method are higher compared to extrusion, some issues do not make this a feasible method of manufacturing. Firstly, this method is very expensive due to the inclusion of some high-precision sensors. Secondly, support structures are required to obtain the best possible surface finish. But if such structures are given, they might change the overall design of the component, and while removing the said structures, deformation of the part might also occur if not done with care. Additionally, the thermal defects that may arise in FDM might also occur here, as no matter how precise the lasers are, some heat will be inevitably transferred to the next layer or point (in the case of TPP). This might cause the deformation of that entity and ultimately affect the whole cell structure of the component.

In addition, there are also many health repercussions. For instance, studies that compared several 3D printers and the toxicity of the by-products thus produced showed that there were several harmful and carcinogenic particles/gases were released due to the burning of plastics (Min et al. 2021). These are referred to as ultrafine particles (UFPs) and volatile organic compounds (VOCs), respectively. When such compounds get trapped in the porous SODFs produced during this process, they cause ailments, like bronchitis, tracheitis, asthma, and cancer, in humans who ingest them. Therefore, to avoid this, the process parameters must be carefully controlled and monitored regularly to minimise the production of such toxic substances. Research has also suggested that the liquid resins, used for production, themselves can be harmful to humans. Additionally, the solvents used in this process are generally corrosive and flammable, which also pose the risk of accidents and, when they come in contact with the skin, cause allergic reactions and dermatitis (Petretta et al. 2019).

2.3 Material Jetting

According to the ISO/ASTM 52900:2021 standard, material jetting is the process in which ‘droplets of feedstock material are selectively deposited’. Also referred to as inkjet printing, this method uses air-excluding tanks that are used to store photopolymer materials, which are heated during their transmission from the storage tank to the nozzle and deposited as drops to form layers on the build platform. Following this, an ultraviolet (UV) light source is used to promote photopolymerisation. The wavelength of this light is determined by the type of monomers/oligomers that have been used to synthesise the respective photopolymer. After the deposition of each layer, the build platform is lowered by a pre-set thickness determined by the operator/manufacturer, which will constitute the resolution of the object made. Since liquid material is used, this process also requires the provision of support structures, especially in regions of overhang, which are removed after printing by unconventional methods such as sonication in a bath of sodium hydroxide solution, heating, or using a high-pressure water jet (Gülcan et al. 2021).

Based on the composition of the resin, inkjet printing can be classified as drop-on-drop (DoD) and drop-on-powder (DoP) deposition methods:

- *Drop-on-Drop:* If the liquefied photopolymer is the building material, then it is termed as drop-on-drop deposition. Generally, a mixture of both the API and excipients is stored in the liquid or molten state. These include but are not limited to polymers, waxes, curable resins, solutions, suspensions, or other multicomponent formulations. This method is more complicated compared to DoP as the droplet size is a major factor in the fabrication. Thus, the rheology of the liquid must be carefully monitored and controlled which is a tedious process. On the other hand, objects produced using this method have a higher resolution as the size of the droplet is 100 μm and can be further reduced by surface wetting, solvent evaporation, or shrinkage. This is less preferred as compared to binder jetting or FDM because the materials used in the process must possess quick gelation properties for the product to be stable, which may not always be the case.
- *Drop-on-Powder:* When a binder solution/suspension/polymer is dropped on a powder substrate to bind them, it is drop-on-powder deposition. This technology was implemented in the fabrication of the first-ever 3D-printed drug, ‘SPRITAM’ (levetiracetam), and plays a major role in the pharmaceutical industry, especially in making SODFs, ever since. This is mainly because the process’s materials (powders and binders) are already used to produce SODFs, which leads to the products having high porosity and friability.

Like any other process, this method also has some demerits. Implementation of this method requires high capital investment, mainly because of the flexibility of the mechanism that must be achieved. This includes the ability of the printhead to handle multiple material bio-inks (plastic and metal-based) and reliability during the performance of high-volume tasks. Another disadvantage is the production of wave-shaped profiles in the final product, in contrast to the smooth profiles printed by a

layer-by-layer mechanism. This is known as the coffee-ring effect and affects the surface finish of the final product (Uddin et al. 2022). Also, provision for control of the drop volume and spacing between them is absent, and as a result, the resolution is low (Tortorich and Choi 2013). This also contributes to the aforementioned defect. In precision pharma applications such as bone tissue engineering and stent manufacturing, there is no tolerance existing for such defects.

There are also potential health hazards for operators, mainly caused due to the UV source used for facilitating photopolymerisation. UV radiation, being classified as a group I carcinogen (Lyon 1994), causes various diseases such as melanoma, carcinoma, and glaucoma and can also adversely affect DNA patterns (Matsumura and Ananthaswamy 2004; Camillo et al. 2022; Ivanov et al. 2018). This can be prevented by attenuating the radiation emitted and by the construction of structures with materials that block such radiation (Zhang et al. 2020).

2.4 Binder Jetting

In this process, a binder solution is jetted into the substrate bed, which helps to promote binding between the particle layers and thus develops a 3D-printed structure. The main components used include a reservoir for storage of binder/ink and powder, a build platform, and a roller to spread the powder substrate. Initially, the powder is discharged onto the build platform, which is then rolled into the desired layer form as deduced from the model. Then, the binder solution is imparted into the printed layer, and the process continues till the entire object is printed. The 3D models for printing are mainly derived from CAD or magnetic resource imaging (MRI) (Basit and Gaisford 2018). This process is identical to drop-on-powder material jetting and is also mainly used in the manufacture of orally ingestible tablets (Sen et al. 2021).

However, achieving consistency and predictability is a major challenge in this process. This arises mainly due to the lack of uniformity during powder deposition. Also, there is shrinkage of each layer after sintering, which causes a variation in thickness between subsequent layers based on the magnitude of shrinkage. This is mainly due to the thermal gradients and distorts the final object. Despite proper infiltration of the binder solution, the porous nature of the powder substrate is not completely removed. This compromises the structural integrity of the final object and makes the material prone to air traps. Particles/gases in the air may react with live cells that may exist in the microstructure and make the material toxic. Since this method is specifically used for SODFs, this makes the 3D-printed tablets inconsumable much before the specified expiry date (Mostafaei et al. 2021; Du et al. 2020).

Other than the above, there also exist certain regulatory challenges. The main use for this process is to produce personalised medicine. But no regulations are currently present to control the drugs thus manufactured. This makes binder jetting not part of good manufacturing practices (GMP). So, regulations are required to control the type of drugs manufactured via this process to prevent misuse of the technology (Basit and Gaisford 2018; Sen et al. 2021).

2.5 Powder Bed Fusion

In this process, a focused power source is used, like a laser or electron beam, to selectively coalesce powdered particles into solid objects. The major advantage of using this mechanism is its ability to fabricate overhanging geometries without provision for separate support structures. This is mainly because the loose powder particles present on the printing platform themselves act as a support. Powder bed fusion (PBF) includes three main processes: selective laser sintering (SLS), direct metal laser sintering (DMLS), and selective laser melting (SLM). The fundamental principle of all the processes is the same (i.e.) layer-by-layer deposition. The characteristic difference between them is the state of the material and the material being sintered or melted. This method finds its application in the aerospace industry (Williams and Revington 2010), the manufacture of automotive and aircraft components (Hettesheimer et al. 2018), flexible electronics (Theodorakos et al. 2015), drug delivery, and healthcare (Awad et al. 2021).

- *Selective Laser Sintering (SLS)*: This process was first patented by Carl Deckard, JJ. Beaman, from the University of Texas, in collaboration with Nova Automation (Beaman and Deckard 1990). It is mainly applied for thermoplastic polymers and the operating temperatures range between 180 and 380 °C (Vock et al. 2019). Since the operating temperatures are very low, the energy is only sufficient to sinter the particles together. In the pharma industry, this process is majorly applied in applications like SODFs and tissue engineering using composite polymers.
- *Direct Metal Laser Sintering (DMLS)*: The extension of the above process to metal particles is termed direct metal laser sintering. However, the production of powdered metal was a challenge that was resolved in 1994 by the Fraunhofer Institute for Production Technology which successfully produced 316L stainless steel powder. Since DMLS is a metal-based process, they are mainly used in the manufacture of alloys, like Ti-6Al-4V, which are difficult to manufacture by conventional processes. This alloy mainly finds its application in orthopaedics, dentistry, and bone replacement applications (Bertol et al. 2010; Rodriguez et al. 2020).
- *Selective Laser Melting (SLM)*: The materials used here are generally metals or ceramics, which are imparted with high energy and are taken up to their melting point. They are then tailored to custom requirements. In 1995, this was first introduced by the Fraunhofer Institute of Technology, which attempted to stretch the boundaries of SLS by patenting a technology that can completely melt metals or ceramics (Meiners et al. 2001).

Although this process possesses some advantages mentioned above, their use to manufacture multidrug SODFs is complex. The challenge mainly arises in the pool monitoring of multi-material objects. The process emissions must be accurately interpreted and applied to each iteration using a control loop. If there occurs a deviation in the process parameters, cross-contamination of powders occurs, which

leads to crack formation and propagation (Binder et al. 2018). The health repercussions of such a failure, especially in human tissue, valve, and muscle substitutes, may be catastrophic. Challenges are also faced in maintaining quality, consistency, and repeatability. If the failure occurs, an alternate product must be manufactured with the same specifications, to precision. But time constraints may cause the improper setting of process parameters and thus compromise the product quality and specs (Vlasea et al. 2015).

3 Need for Quality Control and Good Manufacturing Practices

The superior quality products produced by the pharmaceutical industry are aimed at relieving patients from pain or aiding to cure specific diseases. In order to do so consistently, these products need to not only comply with clinical trial authorisation, i.e. CTA and meet the requirements of the marketing authorisation but also eventually follow certain good manufacturing practices so that these drugs do not place patients at risk. Traditional manufacturing industries have several quality assurance and quality control (QA/QC) tools in place to accurately track the composition and properties of the final material. Similar practices were followed by the European Union as well where they introduced EudraLex Volume 4 (EudraLex 2011), which provides the good manufacturing practices and rules that govern the medicinal products in the European Union.

When it comes to 3D printing, the excipient materials used in drugs, be it polylactic acid (PLA) or others, have been tested significantly. This includes non-destructive tests such as ultrasonic tests, X-ray diffraction, scanning electron microscopy, as well as traditional tests such as metallurgical analyses, chemical and mechanical testing, etc. (Pereira et al. 2017). However, during mass production, it becomes rather difficult to gauge the quality of individual products, and, hence, the concept of quality by design gained significance. Mhatre and Rathore (2009) emphasise that the premise of this quality by design should in fact be based on the understanding of the biology or the mechanism of action of the drug rather than other practices. Elliott et al. (2013) also came up with a guide for implementation for this process.

As the world moves to nanomedicines, opportunities galore as these nanomedicines can break through traditional biological barriers and act as therapeutic agents. In conjunction with 3D printing, these nanomedicines can be used in diagnostic devices and analytical tools and also act as drug delivery agents. Currently over 100 nanomedicines have been approved worldwide by FDA, EMA, etc. as listed by Đorđević et al. (2022). However, there are certain hurdles that deter nanomedicines to make it from the bench to clinic. To start off, appreciating the need for quality requirements of active pharmaceutical ingredients such as these

nanomedicines requires a thorough understanding of three main aspects, i.e. their chemical, physical, and biological properties. This again leads us back to what Mhatre and Rathore (2009) highlighted on quality by design. But with nanomedicine, the most challenging step is not on research but on manufacturing and scale up as research and developmental activities traditionally focus on low-volume production (Paliwal et al. 2014). Using suitable excipients requires a comprehensive understanding of how these nanomaterials can affect not just material properties but also on how it interacts with the excipients itself (Eaton et al. 2015). This therefore requires multiple stages of review and a development portfolio since such process contribute heavily to the overall cost of scaling up towards the final process. Eaton et al. (2015) clearly mention how several companies have gone out of business when they start scaling up and realise the issues related to safety and obtaining the necessary clinical approval as regulations decide how much quantity of this substance can be left back in the human body.

Eventually, these aspects connect back to the manufacturing process as well as the quality of manufacturing, the QA/QC processes, carrying out a risk analysis or FMEA (failure mode effect analyses) and again identifying a design space and doing the necessary design of experiments (DoE) which have been the strengths of the manufacturing industry. This is one place where the Taguchi method and using corresponding orthogonal arrays can prove as a valuable resource for testing since validating nanomedicines can be a costly affair as indicated by Eaton et al. (2015). Once the design of experiments is complete and the design space is verified, one can consider moving to process characterisation, process validation, and process monitoring, the core aspects of quality assurance, and eventually proceed with regulatory filing of this design space.

4 Risks Associated with 3D-Printed Pharmaceuticals to Patients

For years now, discussions have been ongoing on using 3D-printing technologies to manufacture pharmaceuticals. The goal is nearer now with Aprecia Pharmaceuticals winning the FDA approval for ‘SPRITAM’, a novel 3D-printed epilepsy medication that is formulated to rapidly disintegrate in certain conditions (What is Spritam 2023). It must be noted that Aprecia still controls the production and formulation of this drug and has not yet outsourced it for production to other organisations. But in the future, other organisations may come up with similar technologies and could transfer the rights to manufacture such products directly to the physicians which could enable personalised treatment plans for patients. Hence, 3D-printing technology in combination with nanomaterials and customisable drug concentrations can revolutionise the pharmaceutical industry. However, it bodes well to analyse the risks such technologies bring to the fore.

First and foremost, if a pharmaceutical company decides to license its technology to 3D print these drugs locally, the pharmaceutical company must be well aware that it cannot oversee the efficacy of these 3D-printing operations. For example, the material properties of a simple polymer extrusion out of a 3D printer is affected by the nozzle temperature, nozzle diameter, printing speed, platform temperature, printing angle, layer thickness, and filament diameter as well (Hsueh et al. 2021). Combine this with the reliability of the temperature, speed, and angle sensors, a serious threat presents itself as these drugs need to be ingested in our bodies. Any mishaps from consuming these drugs bring about the question on who would be responsible for the aftereffects. Hence, companies need to aim for a legal strategy in such situations.

Secondly, pharmaceutical companies manufacturing these drugs have better control over the entire process. This not only includes the manufacturing parameters but also on how this information transfer happens. In the absence of reliable knowledge transfer media, cyber risks could present itself in multiple forms. It could make such products vulnerable to hackers thereby resulting in a significant magnification of existing risks of such medicines. If the hackers make changes to a drug's recipe or the recommended dosage, this could lead to severe consequences. Further, it could also lead to counterfeits being produced without having a proper understanding of the biology behind such medicines. While pharmaceutical companies can add tracer elements to distinguish their products and add necessary watermarks, the risk posed by such situations need to be thoroughly considered.

Thirdly, the quality of raw materials used for such processes should be thoroughly vetted. The presence of contaminated or defective materials could pose a much serious threat than the 3D printer itself. Further, particle size distribution in raw material can also be a critical aspect as it decides what thickness of layers can be achieved, and it will also give us an insight into the risk of segregation. In addition, if the 3D-printing process is done by binder jetting, the droplet formation depends on the viscoelastic properties as well as the surface tension of the binder solution. This would eventually decide how a drug disintegrates and whether its efficacy can be maintained (Norman et al. 2017).

Lastly, most polymers used in 3D printing also use volatile organic compounds (VOCs) as solvents. When these VOCs and any emitted particles from the 3D-printing process are inhaled by the users, be it physicians or the patients themselves, both are susceptible to a range of side effects including and not limited to allergies, inflammation, asthma, cardiovascular problems, increased risk of oxidative stress, as well as cytotoxic effects like cancer (Min et al. 2021). If the same process produces ultrafine particles, the risk increases tremendously as these particles could get deposited on the respiratory track and eventually enter the bloodstream. As discussed earlier, nanoparticles have the capacity to break traditional biological barriers, and these ultrafine particles could even damage the mitochondria in our bodies (Min et al. 2021) (Fig. 3.1).

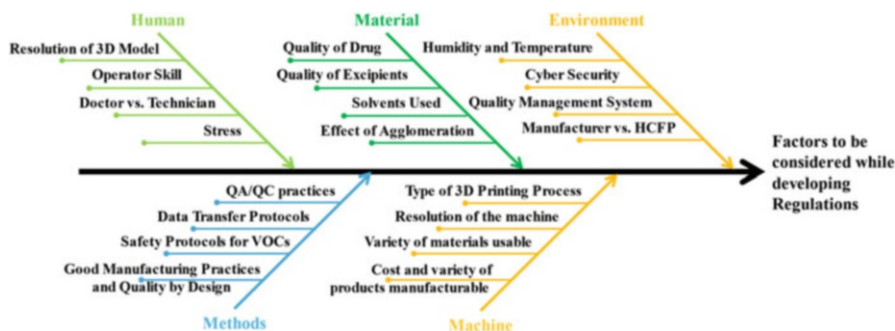


Fig. 3.1 Ishikawa diagram (fishbone) identifying probable risks that need to be considered prior to developing regulations

5 Regulatory Considerations

5.1 Approval Departments

In Europe, the European Medicines Agency (EMA) is in charge of the evaluation and supervision of pharmaceutical products. In addition, the European Medicines Union (EMU) issues specific preliminary guidelines for medicine preparation. Further, the European Chemical Agency (ECA) addresses the use of safe chemicals in manufacturing these pharmaceutical products. However, the European Union currently regulates nanomedicine-based products using risk/benefit analysis principles instead of set guidelines as there is still a lot of unknowns present around 3D-printed drugs and pharmaceuticals (Halamoda-Kenzaoui et al. 2019).

In the United Kingdom, all medicines are regulated by MHRA, i.e. the Medicines and Healthcare Products Regulatory Authority. However, they still lack specific guidelines to both nanotechnology-based products as well as 3D-printed pharmaceuticals. Just like the EU, MHRA also approves such pharmaceuticals on a case-to-case basis.

In Asia, specifically in Japan, Thailand, China, and India, the government bodies are currently working on regulatory guidelines that encompass not only 3D-printed pharmaceuticals but also on other recent technologies that have made its way into the market. For example, the Ministry of Health and Family Welfare in India expanded the definition of 'drugs' to also include those devices whose function is the diagnosis, prevention, and treatment of a disease, which can be correlated to a 3D-printed device as well (M.o.H.a.F. Welfare 2020). Similarly, in Japan, the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency are responsible for this process (Fig. 3.2).

In the United States, the Food and Drug Administration Agency (FDA) is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, etc. They cover both prescription and nonprescription drugs along with vaccines, blood and blood



Fig. 3.2 World-wide drug regulation authorities

products, cellular and gene therapy products, and tissue and tissue-engineered products apart from medical devices, cosmetics, and electronic products used in healthcare. The US FDA has already allowed products like SPRITAM (What is Spritam [2023](#)) which are 3D-printed pharmaceuticals to be commercially sold in the market and is also reviewing such drugs and pharmaceuticals on a case-by-case basis. However, they are also working on a set of guidelines which will be discussed in the coming sections.

5.2 How Can 3D Printing Be Regulated

3D printing or additive manufacturing is merely a process used to prepare a usable product. Regulating the process of 3D printing or regulating 3D printers themselves is unviable as most 3D printers can be used to make several products and not medical devices or pharmaceutical products alone. Furthermore, just like casting, welding, or any of the other numerous manufacturing techniques, 3D printing is simply one of the many ways to manufacture or fabricate an end product. Therefore, neither the process nor the 3D printer itself should be regulated. The question of what can and should be regulated arises at this juncture.

FDA, for instance, does not control or regulate the creation of 3D printers, nor do they regulate the materials being used in 3D printing. They regulate the final 3D-printed product, which may be a device, pharmaceutical product, or biological product based on its characteristics. The three prime factors considered by the FDA in regulation are the actual product type, its intended application or use, and the risk it poses to the users when used in the manner it is intended to be used in. The view of

other regulatory bodies with respect to 3D printing largely remains the same. Some of them do not have a policy dedicated to 3D printing and follow the regulations and guidelines put forth by FDA and CE.

With respect to drugs, the process of regulation between 3D-printed and conventionally manufactured drugs will not vary considerably unless 3D printing affects the overall characteristics or properties of the drug. For example, if 3D printing is used to deposit thin layers of the drug to create multiple layers that may be absorbed at different rates by the body, the final 3D-printed product or drug will be the one regulated unless the process of manufacturing influences the physical, chemical, or biological properties of the aforesaid drug. To understand this better, let us consider SPRITAM, a 3D-printed drug used to treat epilepsy, that was regulated in 2015 (What is Spritam [2023](#)).

In this case, Aprelia found that the dissolution of the pill can be drastically increased by redesigning the drug using 3D printing. This process enabled the creation of multiple layers of drug and makes it porous eventually improving the efficacy of the drug. The required medical effect is, however, achieved by the chemical reaction that takes place given the composition of the drug. Hence in this scenario, as recommended by the practice of quality by design (Mhatre and Rathore [2009](#)) both the manufacturing process and the chemical composition of the drug complement each other and maintain the efficacy of the drug. Thus, instead of regulating the chemical composition of the drug or regulating the process of fabrication, the final product, that is, 3D-printed SPRITAM, is brought under the regulatory framework as a drug.

Hence, the legal and regulatory concerns with regard to 3D printing and its application in medicine are manyfold. It is extremely hard to control the process; however, at the same time, it is pertinent that emphasis be given to the process and the amount of benefit it can provide. Likewise, while it is important that public health is protected, it is also necessary that new drugs that can be delivered in novel ways be developed. Therefore, putting regulations in place, taking account of the considerations is key in maintaining this balance.

The factors highlighted below need to be addressed when considering regulating 3D printing:

1. *Original Product*: Many digital models are built by reverse engineering other existing models. In such a case, the original product or model needs to be accurate. Changes in the same may affect the final product and create a compromise in the efficacy of the drug.
2. *Design/Model*: The model created or designed needs to be accurate. Sometimes, the original product is scaled to create a model. Inaccurate operations may affect the overall efficiency and form of the product, leading to regulatory concerns.
3. *File Quality*: Often the file may be compressed for ease of transmission. This can negatively impact the quality of files, resulting in poor print quality.
4. *3D Printer*: All 3D printers aren't created equal. Some may have poor finish quality, whereas others may ruin the material by heating it. The material in question needs to be compatible with the 3D printer and not alter the composition of the material.

5. *Material*: The material for 3D printing should be considered based on the application. Care needs to be taken to ensure that the material does not get corroded before, during, or after 3D printing.
6. *Operator Skill*: 3D printing involves optimising multiple factors including the feed rate, bed temperature, and so on. Small changes at the operational level can significantly hamper the final output. Therefore, it is extremely important that the operator be aware of the process and the materials thoroughly.

When a drug is being regulated, the above factors may play a prominent role in its development. It is, therefore, of utmost importance that all the factors be considered and optimised for the best output. It is also important that organisations optimise the above factors to be able to scale the production of 3D-printed drugs.

5.3 Proposed Framework for 3D Printing Medical Devices at PoC by CDRH, FDA

Section 201 (h) of the FD&C Act (U. FDA [2017](#)) of US FDA defined a medical device as an instrument, apparatus, machine, implant, and in vitro reagent, including component, part, or accessory that can diagnose, cure, mitigate treat, or prevent disease or condition by affecting the structure or function of the body but at the same time does not achieve the purpose as a drug. In 2020, the US FDA has published a draft on the agency's proposed thinking to introduce regulations of medical devices in general. They classified the devices into three classes based on the degree of risk in entails.

1. The lowest risk group or Class I devices need general controls. This includes labelling, medical device reporting, establishment registration, device listing, quality system, adulteration monitoring, and misbranding monitoring controls in place.
2. For Class II devices, in addition to having the general controls of Class I devices, they also need certain special controls like identification of appropriate design, characteristics or specifications, testing, and special labelling in addition to guidance documents on how to use them and what are the risks that entail in using these Class II devices. Special controls are usually device-specific and include performance standards, postmarket surveillance, patient registries, and premarket data requirements as well.
3. Under federal law, Class III devices are subject to approval of a Premarket Approval Application (PMA). Devices that are not within a type marketed before the date of the Medical Device Amendments of 1976 – referred to pre-amendments devices – are classified into Class III automatically under federal law. In addition, the FDA classifies a device into Class III devices if it is intended to be used in supporting or sustaining human life or preventing impairment of

human health, or that may present a potential unreasonable risk of illness or injury for which general controls and special controls are insufficient to provide reasonable assurance of the safety and effectiveness of a device, or for which there is insufficient information to make such a determination.

Van Norman has documented the approval process of drugs and medical devices by FDA quite well in his work on Drugs and Devices, and the FDA published as Part 1 for Drugs (Van Norman Gail 2016a) and Part 2 for Devices (Van Norman Gail 2016b).

In 2020, the US FDA, specifically the Centre for Devices and Radiological Health (CDRH), in collaboration with the American Society of Mechanical Engineers (ASME) gave an insight into how 3D printing medical devices can be regulated at the Point of Care (PoC) (Joel Anderson et al. 2023). According to FDA, this framework is expecting feedback from public, and once the feedback is consolidated and corresponding inclusions/changes are done, it would go official. They highlighted five different scenarios and proposed certain measures and considerations for each scenario (Fig. 3.3):

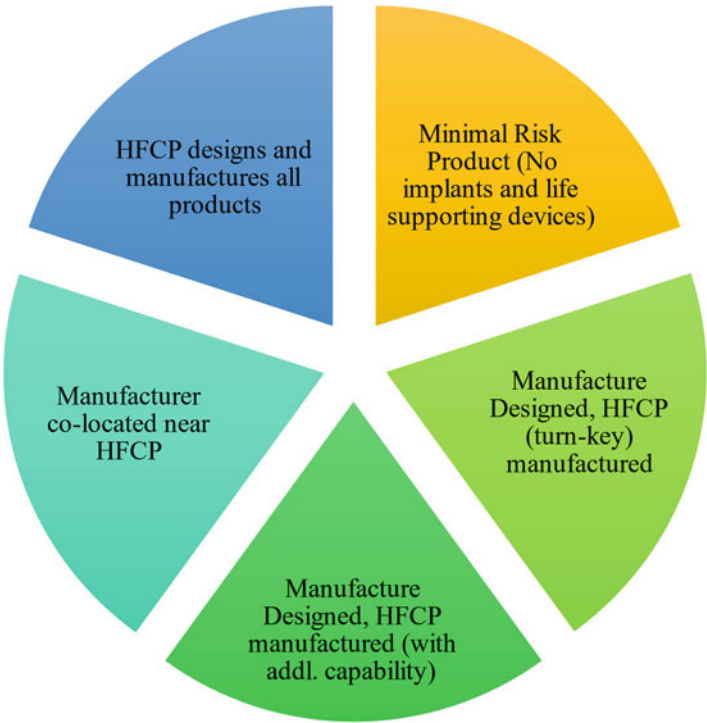


Fig. 3.3 The five scenarios identified by US FDA

1. *Minimal Risk 3DP by Healthcare Facility Prints (HCFPs)*: In this situation, presence of minimal risk in terms of patient safety and ability to print can essentially bring about process monitoring and simple risk mitigation strategies using existing standards and certifications. However, this approach would not be applicable to implants and life-supporting devices that present a serious risk to patients.
2. *Device Designed by Manufacturer Using Validated Process with Turn-Key System*: This is possible when the device is designed by the manufacturer, but it is meant to be printed by the healthcare facility where the post-processing steps are automatic or self-contained. In these situations, it would make sense to use a validated process evaluated by FDA and that can help the device be consistent with cleared indications and manufacturer instructions to use.
3. *Device Designed by Manufacturer Using Validated Process with Additional HCFP Capability Requirements*: When the post-processing steps are more complicated, then the healthcare facility would need to have appropriately trained staff to work on the equipment. This would also bring about the necessity to properly label, train, and instruct the users for calibration, testing, and facilitating the process of 3D printing.
4. *Manufacturer Colocated at Point of Care*: This would be the ideal case scenario as the healthcare facility need not set up or manage their own 3D-printing facility. The FDA can appropriately assess the risk of the 3D-printed drug or device and carry out routine checks with the manufacturer itself. This would therefore require more investment on the manufacturer's part than on the healthcare facility side.
5. *Healthcare Facility Becomes Manufacturer*: This situation arises when the healthcare facility desires to design and control their own 3D-printing operations though the devices are not at minimal risk. This essentially means the healthcare facility should be responsible for development, design, testing, printing, documentation, and all other regulatory requirements. A good example of where such situations could arise is in a university hospital where the doctors and researchers can work together to provide all the necessary solutions.

6 Conclusions and Future Scope

3D printing is an interesting approach as the process can be automated, and one can achieve a layer-by-layer design that can help in dissolution of drugs efficiently. It can also produce customised products depending on the needs of the patients. The commercial feasibility and regulatory approvals need to be worked out for many drugs. However, on the technical side, it is a worthy approach as illustrated by Aprelia's SPRITAM (What is Spritam [2023](#)). FDA ensures that the drugs are in accordance with relevant regulations, especially the current chemistry, manufacturing, and control standards (CMC). When it comes to medical devices and implants, for over 15 years, the FDA has cleared many 3D-printed non-implantable and implantable devices using the 510(k) process. Till 2017, over 75% of the cleared

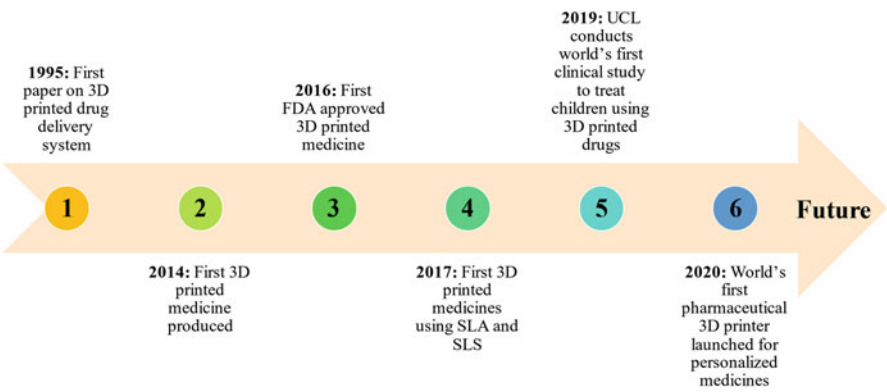


Fig. 3.4 A brief timeline of events

medical devices were orthopaedic implants with others belonging to surgical, dental, and other applications (Coburn and Grant 2017). These implants can also contain drug reservoirs which can enable a controlled release of the drug instead of needing regular injections at the site of surgery (Fig. 3.4).

At the end, however, the risk profile of each product and process needs to be identified as these parameters will dictate what measures are necessary to ensure that the products are safe for human beings and animals alike. Additive manufacturing standards such as ASTM F42, ASTM 52900, etc. can help in regulation of the process parameters. Considering effective QA/QC processes and ensuring a good quality management system will aid in quality by design pharmaceutical manufacturing and lead to translation of clinical trials into commercial products.

As the utilisation of 3D-printing techniques evolve, several new businesses would bring about improved therapies. We may see printers and printheads developed for specific products rather than having one-printer-fits-all solutions. Every government organisation, be it in the United States, Europe, or other countries have their innovation teams and websites that can track emerging technologies and provide necessary assistance on how to get their products certified for commercial purposes. It is a good practice to gain insight from such websites and publications. Contacting the government organisation early in the design or development process can help streamline submission, logistics, experimental design, and trial design thereby enabling a quicker translation to commercial applications. The following chapters are aimed at providing valuable insight into some of the topics discussed in this chapter and will highlight a whole range of possibilities that can arise from it.

Choose the Correct Option

1. In FDA, _____ drugs/devices are subject to approval of a Premarket Approval Application (PMA).			
(a) Class I	(b) Class II a	(c) Class II b	(d) Class III
2. _____ is the first prescription drug product approved by the US Food and Drug Administration (FDA) that is manufactured using 3D-printing technology.			
(a) SPRITAM	(b) TEPOTINIB	(c) KEYTRUDA	(d) AYAHUASCA

(continued)

3. The FDA has approved many 3D-printed non-implantable and implantable devices using the _____ process.			
(a) 270 (a)	(b) 510 (k)	(c) 110 (z)	(d) 179 (r)
4. In the European Union, the _____ addresses the use of safe chemicals in manufacturing these pharmaceutical products.			
(a) European Medicines Agency (EMA)	(b) European Medicines Union (EMU)	(c) European Chemical Agency (ECA)	(d) Medicines and Healthcare Products Regulatory Authority (MHRA)
5. Inhalation of _____ can cause a range of side effects, including allergies, inflammation, asthma, cardiovascular problems			
(a) Volatile Organic Compounds	(b) Herbal Concoctions	(c) Stable salts	(d) None of the above

Determine Whether the Following Statements Are True or False

6. Class I products are exempt from the regulatory process.
7. The first 3D-printed drug that got regulatory approval was used to treat the common cold.
8. The quality of raw material does not impact the final product.
9. Particle size/droplet size of raw material may impair the final surface finish of the product.
10. The FDA regulates the production of 3D printers.

Answer Key

- (1) d; (2) a; (3) b; (4) c; (5) a;
 (6) True; (7) False; (8) False; (9) True; (10) False.

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Chapter 4

Printability of Pharmaceutical Polymers: Issues and Solutions



Ioan Tomuta and Alina Porfire

Abstract 3D printing offers nowadays great potential for the manufacture of pharmaceutical dosage forms. Despite the advantages provided by this technology, there is still a lack of pharmaceutical-grade suitable feedstock materials designed especially for 3D printing. From the perspective of the raw materials used, the proposed printing methods have a common element, namely, polymers. The polymers are used either alone or as blends with other pharmaceutical excipients, usually utilized for manufacturing of dosage forms using conventional technologies. This chapter provides an overview of polymers used in 3D printing applications for dosage forms manufacturing. The polymers relevant to these applications are described by highlighting their general applications in pharmaceutical technology, structural information, physicochemical characteristics, and suitability for 3D printing applications. Besides their general description, a section is dedicated to the presentation of the printability issues of the polymers according to the printing method, as well as the main solutions proposed in the scientific literature to overcome these issues. This material provides a general guide for the selection of the starting material according to the chosen printing method, for those interested in applying 3D printing in the manufacture of pharmaceutical dosage forms.

Keywords Pharmaceutical polymers · Printability · Three-dimensional printing · 3DP · Fused deposition modeling (FDM) · Hot-melt extrusion (HME) · Selective laser sintering (SLS) · Stereolithography (SLA)

1 Introduction

3D printing is a method of manufacturing in which materials are deposited onto one another in layers to produce, in the end, a three-dimensional object. In the pharmaceutical sector, despite considerable innovations and increased number of published

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papers in the last 10 years, a lot of knowledge and progress are needed until the technology may be widely used to prepare pharmaceutical formulations.

One of the major challenges limiting its use is the lack of pharmaceutical-grade suitable feedstock materials designed especially for 3D printing. Generally, polymers alone or in blends with other pharmaceutical excipients were used as feedstock materials. Polymers are the key constituents in manufacturing of pharmaceutical solid dosage forms in both conventional and 3D printing technology. In conventional manufacturing technologies, they are generally used as diluents or fillers, binders, disintegrants, lubricants, coating agents, solubilization enhancers, drug release modifiers or controllers, etc. in tablets and capsules and as rheology enhancers of the solvent, emulsifying agents, suspension agents, etc. in semisolid and liquid preparations (Thakur and Thakur 2015a, b; Ulery et al. 2011). Regarding the 3D printing in medicine, one of the major concerns, in addition to the accessibility of biodegradable, biocompatible, and physically and chemically stable feedstock materials, is the compatibility of those materials with 3D printing technology (Lamichhane et al. 2019; Ligon et al. 2017).

Polymers are substances or materials consisting in large molecules named macromolecules composed of repeating structural units (monomers). According to their origin, they may be either naturally occurring, semisynthetically modified, or synthetically manufactured (Thakur and Thakur 2015b; Pereira et al. 2020). They are obtained via polymerization of many small molecules known as monomers. Due to the large molecular mass of the polymer molecule relative to small monomers, they possess specific physical properties, such as toughness, high elasticity, viscoelasticity, and a tendency to form amorphous and semicrystalline structures. A wide range of polymeric materials has been used in pharmaceuticals for decades, starting with natural ones and continuing with semisynthetic and synthetic ones. Manufacturing of classical dosage forms and modern drug delivery systems is based on biocompatible and biodegradable polymers that are the result of the rapid evolution of some highly topical research areas such as materials science, pharmaceutical technology, nanotechnology, nanomedicine, bioinformatics, and in silico modeling (Thakur and Thakur 2015a; Koo 2017).

There are many 3D printing technologies, known as additive manufacturing technologies, that have been explored for the development and manufacturing of drug products. The most reported technologies are based on material extrusion, inking, powder agglomeration, and photopolymerization, each of them with their particularities, advantages, and disadvantages (Varghese et al. 2022; Lim et al. 2018; Brambilla et al. 2021):

- *Material extrusion*: fused deposition modeling (FDM), semisolid extrusion (SSE), pneumatic or syringe extrusion (PE/SE), and pressure-assisted microsyringe (PAM).
- *Inkjet printing*: drop-on-demand (DoD) and drop-on-powder (DoP).
- *Powder agglomeration*: selective laser sintering (SLS), selective laser melting (SLM), multijet fusion (MJF), and electron beam melting (EBM).
- *VAT-polymerization*: stereolithography (SLA), digital light processing (DLP), and photopolymerization (PP).

In material extrusion 3D printing, the process implies extrusion at a specific temperature with a predefined rate and pressure. In FDM 3D printing, the thermoplastic material melted in a semiliquid state is extruded through a nozzle that can be moved in different directions and deposited layer by layer onto a building platform and then allowed to harden and solidify by reducing its temperature. FDM using commercial 3D printers to print filaments prepared by hot-melt extrusion (HME) of powder blends consisting of active substance and pharmaceutical polymers represents the most reported printing technology in the development of pharmaceutical dosage forms in recent years (Pereira et al. 2020). The polymers used in this technology were originally introduced in the pharmaceutical technology for their role as binders, disintegrants, coating agents, drug release modifiers, and viscosity enhancers, and 3D printing is just a new application of these known materials. The appropriate physicochemical characteristics of carriers used in FDM are thermal stability, good miscibility with the drug, and adequate melt viscosity. Often, they may not have the ideal attributes for this new application, or they possess these attributes as pure substances but in blend with the active substances the initial characteristics are changed. For example, polyvinyl alcohol and polylactic acid have appropriate attributes to be extruded into filaments by HME and printed by FDM, but loaded with active substances, the obtained filaments may be too brittle or too soft to be printed. Thus, the addition of other pharmaceutical excipients in the powder blend to correct those processing shortcomings is needed (Nashed et al. 2021; Bandari et al. 2021).

Inkjet printing was the first printing technology used in the pharmaceutical area for medicine manufacturing and the technology principle consists in specifically and selectively jetting a liquid material containing the active substance onto a substrate. The main steps of the printing process are: (1) generation of the ink droplets, (2) deposition of the droplets on a substrate, and (3) solidification of the droplets on the substrate. Once the first layer of droplets is solidified on the substrate, a new layer is produced on the top, and all the previous steps are followed and repeated until the final formulation is manufactured (Brambilla et al. 2021; Infanger et al. 2019). This technology uses pharmaceutical polymers as binders (i.e., polyvinylpyrrolidone, hydroxypropyl cellulose) but including binders and active substances in the printing ink may cause nozzle clogging, so they are preferably included in the solid substrate. The viscosity of the binders may influence not only the viscosity of the ink formulation but also the disintegration time and dissolution properties of the dosage forms (Infanger et al. 2019; Cader et al. 2019).

The application of VAT polymerization technologies in drug manufacturing is limited by the availability of photopolymerizable monomers/oligomers biocompatible and approved for human use. Another drawback of these methods is related to primarily operate with single materials, so the fabrication of pharmaceutical formulations with multiple materials, such as complex drug-loaded structures or polymer blends, is limited (Palo et al. 2017).

This chapter aims to provide an overview of the pharmaceutical polymers used in 3D printing applications for the manufacturing of dosage forms. In the first part, the most used polymers are described regarding the structural information,

physicochemical characteristics, and their general applications in pharmaceutical technology followed by the suitability and limitation for 3D printing applications. The second part is focused on the main issues and solutions related to the use of polymers in 3D printing for the manufacturing of pharmaceutical formulations.

2 Pharmaceutical Polymers for 3D Printing

2.1 Polyvinyl Alcohol

Polyvinyl alcohol (PVA) is a semicrystalline and hydrophilic synthetic polymer, widely used as an excipient for the preparation of tablets, topical formulations, ophthalmic formulations, or implants. It is considered a safe pharmaceutical excipient being listed both in the United States and European Pharmacopoeias. It is classically used as stabilizing agent in emulsions, viscosity-increasing agent for ophthalmic formulations, and film-forming agent for tablets (Macedo et al. 2020).

More recently it has been used as release-modifying excipient and solubility enhancer via hot-melt extrusion for oral solid formulations or appropriate matrix for fabrication of good drug-loaded filaments in 3D printing (Pereira et al. 2020).

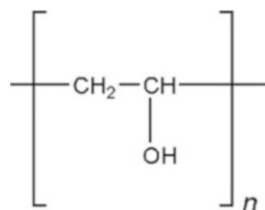
The molecular formula of PVA is $(C_2H_4O)_n$, where a value of n between 500 and 5000 gives commercially available materials with a molecular weight range between 20,000 and 200,000 and different viscosity grades: low viscosity (molecular weight $\sim 20,000$), medium viscosity (molecular weight $\sim 30,000$), and high viscosity (molecular weight $\sim 200,000$) (Paul et al. 2020). The structural formula is presented below, in Fig. 4.1.

PVA is a linear polymer that exists as a copolymer of vinyl alcohol and vinyl acetate, its physical properties being associated with the ratio of the two monomers, the method of preparation, tacticity, the degree of polymerization, and the degree of hydrolysis (Muppalaneni and Hossein 2013).

The degree of polymerization controls the molecular weight of PVA and influences the viscosity of aqueous solutions, whereas the degree of hydrolysis is controlled by catalyst concentration, reaction temperature, and reaction time and influences mainly the solubility in water (De Jaeghere 2016; Erbil 2000).

As the degree of polymerization and the degree of hydrolysis can be controlled separately, several grades of PVA with different physical properties are available for different applications. According to the degree of hydrolysis (DH), PVA is classified

Fig. 4.1 Structural formula of polyvinyl alcohol. (Paul et al. 2020)



as fully hydrolyzed (97.5–99.5% DH) and partially hydrolyzed (80–97.5% DH). According to the degree of polymerization (DP), different viscosity grades of PVA are available based on the viscosity of a 4% aqueous solution of PVA at 20 °C: low viscosity grade (5 mPa.s, PVA with DP ~ 500); medium viscosity grade (20–30 mPa.s, PVA with DP ~ 1700); high viscosity grade (40–50 mPa.s, PVA with DP ~ 5000) (De Jaeghere 2016).

The solubility in water of PVA depends mainly on the degree of hydrolysis and only to a small extent on the degree of polymerization. The high number of hydroxyl groups available in fully hydrolyzed PVA theoretically determines a high affinity to water and high aqueous solubility, but strong hydrogen bonding between intra- and intermolecular hydroxyl groups greatly lower its aqueous solubility. So, fully hydrolyzed PVA (e.g., DH < 99%) is only slightly soluble in water, and heating to over 80 °C is necessary for complete dissolution, while partially hydrolyzed PVA (e.g., DH < 96%) is almost completely soluble at 40 °C. At 20 °C, a sharp reduction of solubility is observed with increasing the degree of hydrolysis; however, partially hydrolyzed PVA (DH < 88%) is almost completely soluble at this temperature (De Jaeghere 2016; Kuraray Poval 2022; Sekisui Chemical 2022).

Other physical properties like resistance to solvents, tensile strength, adhesive strength, and film-forming are enhanced with increased degree of polymerization (consequently increased molecular weight) and degree of hydrolysis (Muppalaneni and Hossein 2013). The fully hydrolyzed grades are recommended to be used when maximum water resistance and humidity resistance is needed.

Regarding the processability in HME and FDM the melting point and the glass transition of the filament/matrix-forming polymer is important. The melting point and glass transition temperatures of PVA primarily depend on the degree of hydrolysis and tacticity (Muppalaneni and Hossein 2013; Kuraray Poval 2022). Unplasticized PVA has melting point around 230 °C for fully hydrolyzed grades, 180–190 °C for partially hydrolyzed grades and displays glass to rubber transition at 58–85 °C (Muppalaneni and Hossein 2013; Kuraray Poval 2022; Sekisui Chemical 2022).

PVA is known as a semicrystalline water-soluble polymer, the degree of crystallinity being mainly influenced by the degree of hydrolysis and less by the degree of polymerization. Generally, a higher degree of hydrolysis leads to a higher crystallinity tendency. In the same time, crystallinity may be changed under external factors, and it is particularly susceptible to increase with the heat treatment temperature (Kuraray Poval 2022). Regarding the degree of hydrolysis, the ability of PVA to crystallize upon heat treatment is affected by the presence of acetate groups, PVA grades with high degree of hydrolysis being difficult to crystallize (Hassan and Peppas 2000).

Due to the spinning properties, high mechanical strength and elasticity, thermostability (degrades above 250 °C), and ability to stabilize amorphous solid dispersions, PVA is a promising candidate for hot-melt extrusion (HME) and fused deposition modeling (FDM) 3D printing (Pereira et al. 2020; Macedo et al. 2020).

PVA is one of the classical polymers used in quick prototype FDM-3D printing as structure material when extremely complex architectures or ones with partially

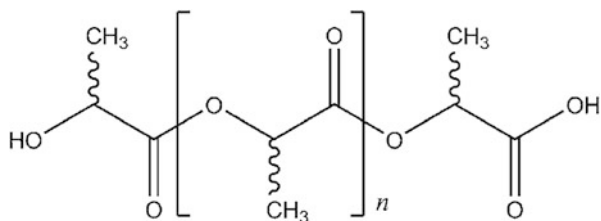
enclosed cavities need to be printed. In this situation, after printing, the PVA structure is easily removed by dissolution in warm water. The commercial PVA filaments for 3D printing are obtained from a blend of different PVA grades to improve the thermal stability and printability and to obtain a less sensitive to humidity material. On a scale from 1 to 10 the PVA filaments have medium printability (5/10), high strength (9/10), low stiffness (3/10), and good durability (7/10) properties. The melting temperature of the product is 163 °C, and the recommended printing temperature is 180–205 °C. Since PVA filaments are moisture sensitive, they should be stored in an airtight container with silica at room temperature in dry conditions. If it is not stored in proper conditions, the PVA filaments that have absorbed humidity from the air will tend to bubble and crack during printing. Those filaments are recommended to be used only after drying in a dehydrator or in an oven for a few hours (Simplify3D [n.d.](#); Product Specification [n.d.](#)).

Loading the commercial PVA filaments with active substances by the soaking method was one of the first methods used for the preparation of oral dosage forms by FDM-3D printing (Tagami et al. [2017](#); Goyanes et al. [2014, 2015](#)). The drawback of this preparation method is the low drug loading ratio achieved (under 0.5%) (Goyanes et al. [2014, 2015](#)). The main advantage is that printing properties of the filament remain almost unchanged.

Filaments with higher drug loading can be obtained by hot-melt extrusion (HME), when drug loading can reach up to 40% (Pereira et al. [2020](#); Saviano et al. [2019](#)). The printing properties of the obtained filament depend on the characteristics of active substances and % of drug loading, and often the use of plasticizers must be considered in order to decrease the brittleness and to increase the printability of the filament (Wei et al. [2020](#)). The printability of drug-loaded PVA filaments may also be influenced by the moisture content. For example, paracetamol-loaded filaments with low moisture are unsuitable for printing due to high brittleness. The storage conditions influence the mechanical properties; the moisture increase acts as a plasticizer and improved the feeding performance on the printer and printability of these filaments after storage (Macedo et al. [2020](#)).

Many authors have used PVA as filament/matrix-forming polymer to manufacture drugs via 3D printing with different release profiles. The processing parameters as extrusion and printing temperatures can vary according to the drug loads and the characteristics of active substances to be processed, and a plasticizer is needed to increase the processability. A tailored drug release profile can be modulated by the combination of formulation factors as PVA grade/plasticizer type and proportion/drug ratio that offer an immense possibility of use. The major drawbacks of PVA in 3D printing are only low miscibility with some drugs requiring high handling temperatures in HME/FDM, even if plasticizers are used.

Fig. 4.2 Structural formula of poly lactic acid. (Paul et al. 2020)



2.2 Poly Lactic Acid (PLA)

Poly(lactic acid) or polylactide (PLA) is a synthetic biodegradable aliphatic polyester, consisting of a racemic mixture of D and L lactide. The empirical formula is $(C_3H_4O_2)_n$, and the molecular weight varies with the desired physical, thermal, mechanical, and degradation characteristics according to the intended application (Paul et al. 2020; Farah et al. 2016). The structural formula is shown below in the Fig. 4.2.

PLA can be prepared from lactic acid by different polymerization methods such as polycondensation, ring-opening polymerization or by direct methods like azeotropic dehydration and enzymatic polymerization. Lactic acid (2-hydroxypropionic acid), the main constituent unit of PLA, is a chiral molecule and exists as two optical isomers (L- and D-lactic acid), so, PLA has four stereoisomers: poly(L-lactide), PLLA; poly(D-lactide), PDLA; poly(D,L-lactide), PDLLA; and meso-poly(lactic acid) (Farah et al. 2016; Borandeh et al. 2021). Among them, only PLLA and PDLLA have been extensively studied and are often used in pharmaceutical applications. PLLA has Tg of 60–65 °C, melting point of 175 °C, mechanical strength of 4.8 GPa, and high-molecular-weight, showing slow degradation. PDLLA has slightly lower Tg of 55–60 °C and lower mechanical strength of 1.9 GPa and possesses more desirable degradation properties than PLLA (Ulery et al. 2011; Borandeh et al. 2021). Under dry conditions, PDLLA is stable. According to the molecular weight, it typically biodegrades over a period of 10–15 months. Increasing temperature and moisture enhances biodegradation, in water at 25 °C it is shortened to 6 months (Paul et al. 2020). Degradation products of PLA are nontoxic making it a natural choice for pharmaceutical and biomedical applications, being also approved by FDA for direct contact with biological fluids (Ulery et al. 2011; Farah et al. 2016).

PLA mechanical properties may vary in a large range from soft and elastic plastics to stiff and high strength materials. Semicrystalline PLA is preferred when higher mechanical properties are needed. It has a tensile modulus of approximate 3 GPa, a flexural modulus of 5 GPa, a tensile strength of 50–70 MPa, a flexural strength of 100 MPa, and an elongation at break of about 4% (Farah et al. 2016).

PLA is commonly used in pharmaceutical applications to prepare drug delivery films, implants, and oral solid dispersions and in tissue engineering to manufacture scaffolds, tendons, cartilages, bones, or for vascular regeneration. To obtain composites materials with desirable properties, it is often combined with other

biodegradable polymers such as poly(caprolactone), poly(ethylene glycol) – PEG, poly(lactide-co-glycolide) – PLGA, chitosan or collagen (Ulery et al. 2011; Paul et al. 2020).

PLA is one of the most popular materials used in *desktop FDM-3D printing* for rapid prototyping, and it is the filament of choice because it is easy to print, not very expensive, and allows to create parts with a wide variety of shape and applications. Due to its biodegradable properties, it is one of the most environmentally friendly filaments on the market. The commercial PLA, filaments for 3D printing are available in standard type or enhanced with special additives to increase their performance, usually concerning strength and durability. On a scale from 1 to 10, the standard PLA filaments have high printability (9/10), good strength (7/10), good stiffness (7.5/10), and low durability (4/10) properties. The product has melting temperature of 175 °C and the recommended printing temperature is 190–220 °C (Simplify3D n.d.; Heidari-Rarani et al. 2019). It was one of the first materials used to prepare custom-made feedstock material for 3D printing of pharmaceutical drug products with controlled release (Boetker et al. 2016).

PLA is a hydrophobic polymer widely used in FDM-3D printing due to its good thermal and mechanical characteristics. Usually, a formulation containing PLA is used to produce extended-release patterns for drugs, but theoretically, based on its biocompatibility, adequate mechanical properties, and high printability, this polymer can be used to manufacture almost all drug delivery systems by FDM-3D printing, via fused deposition modeling, including transdermal drug delivery systems (Durga Prasad Reddy and Sharma 2020), vaginal rings (Borandeh et al. 2021), and implants (Manini et al. 2022). The limitations are related only to thermal stability of the active substances (Nashed et al. 2021; Borandeh et al. 2021).

2.3 Cellulosic Polymers

Cellulose is a natural polymer (polysaccharide), composed of glucose units, generally synthesized by plants. It is found in most plants, mainly in leaves and stems, but only cotton fibers and wood are the primary sources of cellulose for industrial application. Its main properties of interest are biodegradability and resistance to hydrolysis. Cellulose and cellulose derivatives have a wide range of applications in the paper, clothing, food, cosmetic, or pharmaceutical industries (Ibrahim et al. 2019; Funk et al. 2022). Microcrystalline cellulose is one of the most widely used excipients in the pharmaceutical sector in oral solid formulations (tablets and capsules), primarily as a binder/diluent, both in wet granulation and direct compression. It also has some lubricating and disintegrating properties that make it very useful in tableting (Paul et al. 2020).

Microcrystalline cellulose is insoluble in water and most organic solvents due to its crystalline structure, conferred by strong intermolecular hydrogen bonding. Although it has good mechanical properties, its very high melting point (around 450 °C) makes it very difficult to use in hot-melt extrusion or 3D printing.

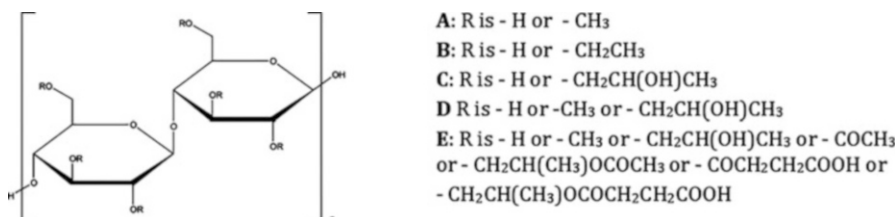


Fig. 4.3 Structural formula of cellulose ethers derivatives (Paul et al. 2020). A: methylcellulose (MC), B: ethyl cellulose (EC), C: hydroxypropyl cellulose (HPC), D: hydroxypropyl methylcellulose (HPMC), E: hydroxypropyl methylcellulose acetate succinate (HPMC-AS)

Etherification and esterification of hydroxyl groups in the glucose ring are the strategies used to change cellulose's physicochemical and mechanical properties. At the same time, properties such as plasticity and solubility are affected by the degree of substitution (DS) and molar substitution (MS). The DS is the average number of hydroxyl groups in the glucose ring replaced by substituents, and MS is the length of the side chains. An increase in DS by nonpolar groups or MS increases the plasticity of cellulose derivatives. Generically, cellulose ether derivatives are water-soluble polymers, while cellulose esters derivatives display hydrophobic properties. The water solubility of cellulose ethers is affected by the DS; with an increase in DS, the solubility gradually shifts from dilute alkali to water and finally to an organic solvent. Regarding the MS, cellulose ethers with moderate and high molecular weights are insoluble in water (Funk et al. 2022; Giri et al. 2021).

Cellulose derivatives are widely used in the pharmaceutical sector as binders, disintegrants, film-coating or controlled/sustained/extended-release matrix formers in tablets, and thickening agents in topical preparations, suspending agents in oral liquid formulations (Paul et al. 2020).

Carboxymethyl cellulose (CMC), methylcellulose (MC), ethyl cellulose (EC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), and hydroxyethyl cellulose (HEC) are the most used cellulose derivatives in pharmaceutical formulations (Funk et al. 2022; Giri et al. 2021). The structural formula of cellulose ethers derivatives is shown below, in Fig. 4.3.

In 3D printing, cellulose derivatives have been used as matrix-forming agents or as binders and disintegrants to tailor the drug release kinetics. Some of the commonly used cellulose derivatives in the pharmaceutical 3D printing are discussed below.

2.3.1 Ethyl Cellulose (EC)

Ethyl cellulose is a partially substituted poly(ethyl)ether of cellulose. In EC, some of the hydroxyl groups of cellulose have been replaced with ethyl-forming $-OCH_2CH_3$ groups. Generally, EC is partially ethoxylated and grades with complete ethoxyl

substitution have the degree of substitution (DS) 3 (Paul et al. 2020). According to the level of replacement of the hydroxyl with ethoxy substituents, several different grades of EC are available: G-grade (44.5–45.5%), K-grade (45.5–46.8%), N-grade (47.5–49.0%), and T-grade (>49.0%) (Pereira et al. 2020).

EC is practically insoluble in water, glycerine, and propylene glycol. EC grade that contains less than 46.5% ethoxy groups is freely soluble in methanol, ethanol, methyl acetate, ethyl acetate, chloroform, tetrahydrofuran, or mixtures of aromatic hydrocarbons with ethanol (Paul et al. 2020).

EC is used in the pharmaceutical sector as coating agent and binder in tablets and as viscosity-increasing agent or thickening agent in topical formulations (creams, lotions, or gels). Primarily, EC is used as a coating agent for tablets and granules to modify the release of the active substance, to improve the stability, or to mask an unpleasant taste. Further, high-viscosity EC grades are used in drug microencapsulation and as matrix former in extended-release tablet formulations (Paul et al. 2020; Colorcon Inc 2019; Ashland Inc 2019).

EC has a Tg of around 130 °C (129–133 °C) and a melting point of around 180 °C, depending on the polymer MW. EC is highly flexible and has considerable mechanical strength, toughness, and film-forming ability or filament-forming ability. High thermostability (degradation temperature is 280 °C), thermoplastic properties, and miscibility with incorporated plasticizers make EC a suitable polymer for 3D printing. Lower viscosity EC grades have better thermoplastic properties than higher MW grades, probably due to better alignment and less steric hindrance in low MW grades (Pereira et al. 2020; Giri et al. 2021).

2.3.2 Hydroxypropyl Cellulose (HPC)

Hydroxypropyl cellulose is a partially substituted poly(hydroxypropyl) ether of cellulose. In HPC some of the hydroxyl groups of cellulose have been replaced with hydroxypropyl forming $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3$ groups. The average number of hydroxyl groups substituted in the glucose ring shows the degree of substitution (DS). A DS of 3.0 means complete substitution. Because the hydroxypropyl group added contains a hydroxyl group that can also be etherified during the preparation process, the number of hydroxypropyl groups per glucose ring can be higher than 3. To have a good solubility in water, the DS must have a value of approximately 4. The low-substituted HPC has only a small proportion of the three hydroxyl groups of the glucose ring substituted and converted to a hydroxypropyl ether (Paul et al. 2020).

HPC has a temperature-dependent water solubility profile; it is soluble in cold water, not soluble in hot water and precipitates as swollen flocs at temperatures between 40 and 45 °C. In organic solvents such as methanol, ethanol, isopropyl alcohol, or acetone HPC is poorly soluble. The aqueous solution of HPC is stable at pH 6.0–8.0, but lowering the pH, acid hydrolysis may occur, with decreasing the solution viscosity, while at increased pH, the alkali-catalyzed oxidation reaction may be induced which conducts to polymer degradation (Giri et al. 2021; Ashland Inc

2017). HPC is a semisynthetic hydrophilic polymer widely used in pharmaceutical industry as binder, disintegrant, film-coating, or extended-release-matrix former in tablets manufacturing, in microencapsulation processes or in topical formulations, for preparation of transdermal patches and ophthalmic products. In cosmetics and in food products, it is used as an emulsifier and stabilizer (Paul et al. 2020; NISSO HPC | Nippon Soda Co n.d.). HPC is commercially available in a number of different grades that have different particle size, different MWs, and varying solution viscosities (Funk et al. 2022; Ashland Inc 2017; NISSO HPC | Nippon Soda Co n.d.). Being available in different viscosity grades and average MW, HPC is suitable for developing drug delivery systems with different release profiles. HPC grade with high molecular weight exhibits high swellability and is suitable for controlled-release matrices, while the ultralow molecular grade HPC shows faster drug release and is suitable for immediate-release formulations (Borandeh et al. 2021; Azad et al. 2020).

Its high thermostability (degradation temperature 227 °C) and thermoplastic properties make HPC suitable for processes that require melting and extrusion, such as fused deposition modeling. Due to molecular mobility complexities in the polymer structure, HPC has biphasic T_g; the first T_g appears roughly at −4.5 °C, while the second is above 100 °C (approximately 110 °C, depending on moisture content). For low MW HPC grade, the extrusion process may be possible at low temperatures as 120 °C, while high MW HPC grade can be processed only at 200 °C (Pereira et al. 2020; Giri et al. 2020, 2021).

2.3.3 Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl methylcellulose, also known as hypromellose, is a hydrophilic polymer, partly O-methylated and O-(2-hydroxypropylated) cellulose. HPMC is a cellulose ether in which one or more of the three-hydroxyl groups present in the cellulose ring have been replaced with methyl-forming −OCH₃ or hydroxypropyl-forming −OCH₂CH(OH)CH₃ groups (Paul et al. 2020; Giri et al. 2021).

The ratio of methyl and hydroxypropyl substitutes has a direct impact on HPMC properties as hydration, swelling and viscosity of aqueous solutions, and thermal gelation temperature of aqueous solutions and consequently on drug delivery performance and intended applications. According to the percentage content of the methoxy group and hydroxypropoxy group calculated on a dried basis, PhEur and USP define four types of hypromellose (1828, 2208, 2906, 2910). The first two digits refer to the approximate percentage content of the methoxy group, while the second two digits to the approximate percentage content of the hydroxypropoxy group (Colorcon Inc 2022a; EDQM 2022). It is commercially available in several grades with different viscosities and degrees of substitution. The commercial grades have the molecular weight in the range of 10–1500 kDa (Giri et al. 2021).

HPMC is a nonionic, hydrophilic, swellable, biocompatible, and biodegradable polymer, properties that make it suitable for a wide range of applications in the pharmaceutical sector. Its high water swellability plays an important role in drug

release kinetics from solid dosage forms (Borandeh et al. 2021). Some HPMC grades are also swellable in ethanol (Paul et al. 2020).

HPMC is soluble in cold water, forming a viscous colloidal solution, but becomes practically insoluble in hot water. Also, it is practically insoluble in chloroform, ether, or ethanol (95%) but becomes soluble in mixtures of water and alcohol, mixtures of dichloromethane and ethanol, or mixtures of dichloromethane and methanol. The ratios of hydroxypropyl and methyl substitution and the degree of substitution are factors which influence the solubility of HPMC in organic solvents. Certain grades are soluble in mixtures of dichloromethane and propanol and mixtures of water and acetone and other organic solvents. Water solutions are stable at pH 3–11. Due to its nonionic nature, aqueous solutions of HPMC are compatible with metallic salts or ionic organics (doesn't form complexes or insoluble precipitates) (Pereira et al. 2020; Giri et al. 2021; Colorcon Inc 2022a, b).

HPMC is one of the most used polymers in pharmaceutical formulations in oral, ophthalmic, nasal, and topical dosage forms. It is primarily used as binder, film-coating agent, extended/delayed-release matrix or drug solubilizer in tablets. In liquid formulations, it is used as a suspending/thickening/stabilizing agent, emulsifying/emulsion stabilizer agent or viscosity-increasing agent in concentrations ranging from 0.25% to 5.0%. In topical formulations it is used as emulsifier and suspending, thickening, and stabilizing agent (Paul et al. 2020; Giri et al. 2021; Colorcon Inc 2022a).

Although HPMC is traditionally used to prepare extended-release matrix tablets via direct compression or granulation technology, it is also a suitable polymer to manufacture 3D-printed dosage forms with immediate-release profiles. By combining different HPMC grades and other excipients (as plasticizers), tablets with different designs and tailored drug release profile can be produced. The drug release from HPMC matrices is very complex, involving three simultaneous processes (polymeric swelling, drug diffusion, and polymer erosion), and the ratio between them is different according with drug solubility. It has been accepted that for hydrophilic drugs, diffusion through the gel layer is the main mechanism of drug release, while hydrophobic drugs reach the dissolution medium mainly after matrix erosion (Funk et al. 2022; Giri et al. 2021; Ghimire et al. 2010).

In pharmaceutical 3D printing, the HPMC was successfully used to prepare solid dosage forms by SLS (Fina et al. 2018a), FDM (Zhang et al. 2017a; Jain et al. 2018), or inkjet printing (Blynskaya et al. 2022). High thermostability (degradation temperature > 250 °C) and thermoplastic properties make HPMC an excellent candidate for extrusion-related processes and one of the best polymers for filaments preparation. But high Tg values (96–145 °C) and high Tm (between 160 and 210 °C) with a relatively high melt viscosity make it difficult to use without plasticizers (Funk et al. 2022; Giri et al. 2021). Consequently, most studies have reported the use of plasticizers such as mannitol, triacetin, triethyl citrate (TEC), and polyethylene glycol (PEG) to facilitate the extrusion process and to obtain filaments with adequate mechanical properties for 3D printing (Giri et al. 2021; Samaro et al. 2020). However, other authors have reported that some drugs with low MW (i.e., glipizide (Khizer et al. 2019) or diltiazem (Kadry et al. 2018)) act as plasticizer, lower the

melting temperature of the polymer-drug blend below the degradation temperature of both the drug and polymer, allowing processing in lower thermal conditions (usual below 180 °C) during HME/FDM (Pereira et al. 2020; Giri et al. 2021; Kadry et al. 2018). To overcome the high thermal processability, DuPont has developed AFFINISOL™ HPMC HME, a hydroxypropyl methylcellulose designed for hot-melt extrusion with the polymer substitution architecture that enables thermal processability. Three commercial grades, with different molecular weights, are available, AFFINISOL™ HPMC HME 15 LV, 100LV, and 4M. Improving the thermal processability is related to lowering the melting point, the AFFINISOL™ HPMC HME having the lowest recommended processing temperature of 135 °C (for 15LV grade), 145 °C (for 100LV grade), or 145 °C (for 4M grade) and lower melt viscosity (DuPont Inc n.d.; Huang et al. 2016). Although DUPONT recommends AFFINISOL™ to formulate stable amorphous solid dispersions (ASDs) with poorly soluble APIs via spray-dried dispersion (SDD) or hot-melt extrusion (HME), it was extensively employed by de researchers to prepare medicines via fused deposition modeling (FDM) (Kadry et al. 2018; Mora-Castaño et al. 2022).

Adequate mechanical and physical properties as water solubility, swelling capacity, thermal stability, nonionic behavior, and high miscibility with drugs make HPMC the most used cellulosic polymer in 3D printing of drugs using different technologies. The wide use is facilitated by the broad range of commercial grades available, with different hydroxypropyl and methyl substitution ratios and various properties as melting point, melt viscosity, hydration, aqueous solution viscosity and swelling capacity (Pereira et al. 2020). As a result, many authors have used HPMC as a filament and matrix-forming polymer to manufacture drugs via FDM-3D printing with tailored release profiles. Melt viscosity and processing parameters such as extrusion or printing temperatures are affected by the characteristics of active substances to be processed, active substances load ratio, and plasticizers are needed to improve the processability. The desired drug release profile can be modulated by the combination of formulation factors such as HPMC grade, drug load, plasticizer type, plasticizer ratio, or printlet size, design, and shape, which offer an immense possibility of combinations (Tidau and Finke 2022; Zhang et al. 2017b).

2.3.4 Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS)

Hydroxypropyl methylcellulose acetate succinate, also known as hypromellose acetate succinate, is a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methyl cellulose. Practically HPMC-AS consists of a cellulose backbone integrated with hydroxypropyl, methyl, acetyl, and succinoyl groups (Paul et al. 2020; Giri et al. 2021; Shin-Etsu Inc 2022).

It was developed by Shin-Etsu Chemical and was first commercialized in 1987 in Japan as an enteric coating agent under the trade name AQOAT®. Currently, nine commercial grades are available, depending on particle size (fine, medium, or granular) and the extent of substitution, mainly of succinoyl and acetyl groups. The commercial grade with predominant fine cohesive particles (size ~5–10 µm)

is F, with medium size particles (between 70 and 300 μm) is MP, while the free-flowing granules sort (particle size ~ 0.5 mm) is G. The extent of substitution and the succinoyl to acetyl substitution ratios (S/A ratio) influence the pH-dependent solubility. The F grade is recommended mainly for aqueous coating, M grade for solid dispersion via hot-melt extrusion, and G for solid dispersion via spray-drying and organic coating (Pereira et al. 2020; Shin-Etsu Inc 2022). According to the solubility, three HPMC-AS commercial grades are distinguished: L dissolves at low pH (≥ 5.5), M dissolves at medium pH (≥ 6.0), and H dissolves at high pH (≥ 6.5) (Shin-Etsu Inc 2022).

HPMC-AS is practically insoluble in ethanol (95%), hexane, xylene, and unbuffered water. It forms a clear or turbid solution in buffers with pH greater than 5.5. The exact pH value at which the HPMC-AS starts to swell and dissolve depends on ionic strength, buffer type, and succinoyl to acetyl substitution ratios, according to the rank order of solubility for the various chemical grades (L, M, H). A clear or turbid viscous solution is obtained in acetone, mixtures of acetone/ethanol (95%), and mixtures of acetone/dichloromethane (1:1). The molecular weight of HPMCAS is approximately 55,000–93,000 Da, and the viscosity varies between 2.4 and 3.6 mPa·s (Paul et al. 2020; Shin-Etsu Inc 2022).

HPMC-AS is widely used in pharmaceutical sector (Paul et al. 2020). In addition to the most used application as film-forming agent in enteric coating, it is used as controlled/sustained-release agent, alone and in combination with other soluble or insoluble binders. The drug release in the gastrointestinal tract can be controlled by using the suitable grade of the polymer. Other application for HPMC-AS is solubility-enhancing agent through solid dispersions prepared via spray-drying. HPMC-AS inhibits drug crystallization in amorphous solid dispersions, leading to enhanced solubility and dissolution of poorly water-soluble drugs (Giri et al. 2021; Debotton and Dahan 2017; Succinate-based et al. 2008).

HPMC-AS is primarily an amorphous polymer with T_g close to 120 $^{\circ}\text{C}$ and moderate melt viscosity. Its high degradation temperature (between 258 and 276 $^{\circ}\text{C}$) and low melting point give it a wider thermal processing window than that of other commonly used cellulosic polymers and make it a suitable polymer for FDM-3D printing (Giri et al. 2021; Sarode et al. 2014). Lu et al. investigated the physico-chemical properties of melt-extruded filaments and found that HPMC-AS is extrudable between a temperature range of 130–180 $^{\circ}\text{C}$ without any notable degradation (Lu et al. 2018). Similar results were found in another study where the processability for 3D printing was studied according to the physicochemical characteristics of different HPMC-AS-grade polymers (LF, MF, and HF), and MF-grade had the best flowing properties, whereas LF-grade was the most stable for thermal extrusion (Sarode et al. 2014). To facilitate the melt-extrusion process by reduction of T_g and melt viscosity, plasticizers are added to a polymer-drug blend. Triethyl citrate as a plasticizer is the most used, being recommended by Shin-Etsu, but also triacetin, different grades of polyethylene oxides (PEO), polyethylene glycol (PEG), Tween[®] 80, stearic acid (SA), or glycerol may be used (Giri et al. 2021; Shin-Etsu Inc 2022; Scoutaris et al. 2018).

One of the main advantages of using HPMC-AS as filament and matrix-forming polymer in 3D printing is the possibility to obtain gastro-resistant tablets directly through FDM 3D printing technology without the need of an enteric coating process (Goyanes et al. 2017).

2.4 Polymethacrylates (Eudragit)

Polymethacrylates are synthetic cationic and anionic polymers described as fully polymerized copolymers of methacrylic acid and acrylic or methacrylic esters. They are known under the brand name Eudragit[®] and are widely used in pharmaceutical formulations as film-coating agents, tablet binders, tablet diluents, solubility enhancers, or matrix layers of transdermal delivery systems (Paul et al. 2020). The structural formula is illustrated in Fig. 4.4.

Polymethacrylates are used individually or in combination, to obtain immediate, accelerated, delayed, sustained, pulsatile, and zero-order release of oral solid dosage forms, including regular or matrix tablets, multiparticulate systems, and hard or soft-gel capsules (Evonik Nutrition and Care GmbH 2019).

Different possible combinations of esters for polymerization lead to several different types, with different solubility characteristics, commercially available. For processing and handling, dry powders, granules, aqueous dispersions, organic solutions, powders, or ready-to-use powders are available. They are compatible with almost all relevant pharmaceutical technologies starting with microencapsulation, spray-drying, granulation (wet, dry, or melt), film coating, and ending with hot-melt extrusion and 3D printing (Paul et al. 2020; Evonik Nutrition and Care GmbH 2019; Thakral et al. 2013).

Dry powders are stable for at least 3 years if stored at temperatures lower than 30 °C in a tightly closed container. Above 30 °C polymer powders tend to form clumps that can be readily broken up. Aqueous dispersions are very sensitive to extreme temperatures. Thus, at temperatures below 0 °C, phase separation occurs; therefore it should be shipped and stored at temperatures between 5 and 25 °C (Sen et al. 2020; Paul et al. 2020).

Eudragit E is a cationic polymer soluble in aqueous solutions below pH 5. Eudragit FS is an anionic polymer composed of methyl acrylate, methyl

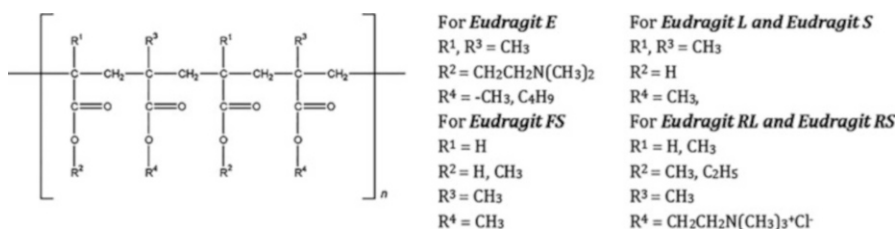


Fig. 4.4 Structural formula of polymethacrylates. (Paul et al. 2020)

methacrylate, and methacrylic acid, available only as 30% aqueous dispersion, presenting low viscosity and solubility above pH 7.0, and used for colonic drug delivery systems formulations. Eudragit L and S are anionic polymers consisting of poly(methacrylic acid-co-acrylates). The difference between Eudragit L and S is the ratio of free carboxyl groups to the ester that is approximately 1:1 in Eudragit L and approximately 1:2 in Eudragit S. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis. Eudragit RL and Eudragit RS are cationic polymers insoluble in water and show pH-independent swelling and permeability properties. The permeability is proved by the ammonium groups in their structure and is more intensely as the amount of ammonium groups increases. So, Eudragit RL is highly permeable, unlike Eudragit RS that has the same molecular structure and the same physical properties, with the exception of its permeability, which is much lower. Having different permeabilities, these two polymers are often used together in different ratios to achieve the specific permeability and the target kinetic release (Paul et al. 2020; Thakral et al. 2013; Patra et al. 2017).

In the last years polymethacrylates were widely explored by many research groups in pharmaceuticals 3D printing as polymeric matrix, taste masking, and coating agent to prepare tablets, capsules, printlets, or patches with immediate or sustained drug release profile. The most used printing technique was FDM via HME. Others explored techniques were direct extrusion (Kuźmińska et al. 2021; Dos Santos et al. 2021) and SLS (Brambilla et al. 2021; Dos Santos et al. 2021).

2.5 Polyvinylpyrrolidone and Copolymers

Polyvinylpyrrolidone (PVP), known as povidone, is a synthetic, nonionic, linear polymer consisting essentially of repeating units of 1-vinyl-2-pyrrolidinone. According to the number of repeating units, different degrees of polymerization are obtained, which will conduct to polymers of various molecular weights (Paul et al. 2020; Kurakula and Rao 2020). Copovidone or 1-vinyl-2-pyrrolidone polymer with vinyl acetate is a copolymer of PVP with improved plasticity properties and low hygroscopicity (BASF – Nutrition and Health 2022). The structural formulas are shown below (Fig. 4.5).

The European Pharmacopoeia describe povidone (PVP) as linear polymers of 1-ethenylpyrrolidin-2-one and copovidone (PVP/VA) as a copolymer of 1-ethenylpyrrolidin-2-one and ethenyl acetate in the mass proportion of 3:2 (EDQM 2022).

Both polymers are broadly used in pharmaceuticals to improve physico-mechanical properties and stability of the formulations as well as drug release rate modifier or to improve drug bioavailability (Luo et al. 2021). They are primarily used in solid oral dosage formulations as binder in tablets and capsules wet granulation or added in the dry form and in situ granulation by addition of ethanol, water, or hydroalcoholic solutions. In tableting copovidone has better plasticity and is less

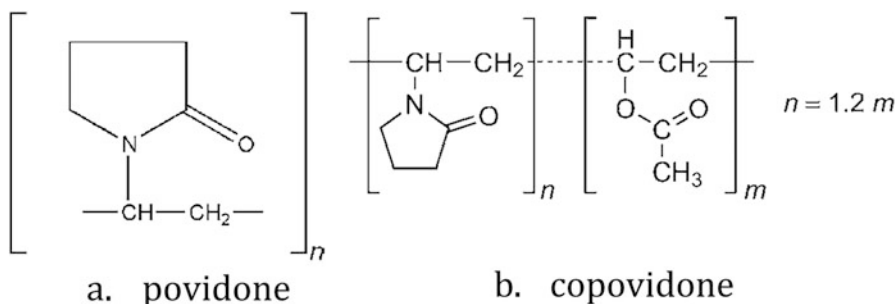


Fig. 4.5 Structural formula of povidone (a) and copovidone (b). (Paul et al. 2020)

hygroscopic than povidone. In direct compression and roller compaction it is used as dry binder, fine powder of cospovidone providing better results than povidone and cellulose derivatives. Povidone and copovidone solutions are also used as coating agent or binder in pellets preparation by powder or suspension layering. As film-forming agent in tablets, coating copovidone provides good elasticity, hardness, and adhesion. As solubilizer, povidone is used to enhance the dissolution of poorly soluble drugs in oral and parenteral formulations. In oral formulations copovidone may also be used to produce amorphous solid dispersions. Additionally, povidone may be used as a viscosity-increasing and suspending agent in topical or oral solutions and suspension (Paul et al. 2020; Kurakula and Rao 2020; BASF – Nutrition and Health 2022; Health B-N 2019).

Povidone is an odorless or almost odorless, white to creamy-white colored, and very hygroscopic powder. Instead copovidone stored at 50% relative humidity gains less than 10% weight. Copovidone has a faint characteristic odor and practically no taste. Povidone is freely soluble in water, and the water solution concentration is limited only by the viscosity of the resulting solution. Povidone is also freely soluble in ethanol (95%), methanol, chloroform, or ketones and practically insoluble in ether, hydrocarbons, and mineral oil. Copovidone readily dissolves in all hydrophilic solvents and is less soluble in ether and hydrocarbons (Paul et al. 2020; Kurakula and Rao 2020; BASF – Nutrition and Health 2022; Health B-N 2019).

The melting point of copovidone is 140 °C and povidone softens at 150 °C (Paul et al. 2020). Glass transition temperature of copovidone is 105 °C and of povidone between 72 °C (grade with low MW, 2000–3000) and 177 °C (grade with high MW 1000000–1,500,000) (Health B-N 2019; Gupta et al. 2014).

In pharmaceutical 3D printing, polyvinylpyrrolidone and copolymers were used as suitable excipients in fused deposition modeling (FDM), selective laser sintering (SLS), semisolid extrusion (SSE), and binder jet technology.

In FDM, pure filaments of povidone are brittle, are less flexible, and were fractured easily under low loads, so they don't have suitable characteristics to be printed through a heated nozzle. Similarly, copovidone, though it is extruded at 150 °C or above, the pure filaments were brittle and could not withstand the 3D printing stress. However, with a suitable amount of triethyl citrate as plasticizer (10–35%),

the filaments of both polymers were successfully 3D printed into immediate-release tablets. The binary blend with triethyl citrate was extruded at temperatures significantly lower than 100 °C and the resulting filaments were used to fabricate immediate-release 3D tablets with pantoprazole at lower temperature (ca. 85 °C) due to inherent flexibility and mechanical strength (Kempin et al. 2018; Ali et al. 2019). Flexibility, brittleness, and mechanical properties of copovidone filaments can also be enhanced by the addition of HPMC or HPMCAS. Copovidone in binary blends with HPMC/HPMCAS loaded with 10% haloperidol was successfully used in the fabrication of 3D-printed tablets through FDM via HME (Solanki et al. 2018). Also sorbitol, polycaprolactone, and polyethylene oxide were found to be suitable materials to improve the flexibility, brittleness, and mechanical properties of povidone or copovidone filaments (Nukala et al. 2019; Fuenmayor et al. 2018). Low processing temperature needed for thermosensitive drugs may be obtained by blending copovidone with low-molecular-weight povidone (Kollidon 12PF) (Kollamaram et al. 2018).

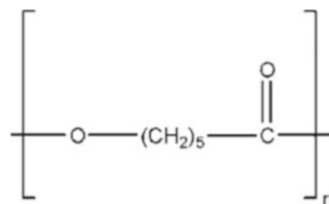
Regarding the suitability for selective laser sintering technology (SLS), copovidone was successfully used to prepare orally disintegrating tablets loaded with paracetamol (Fina et al. 2018a) and ondansetron (Allahham et al. 2020), with pore structure that assures disintegration time of about 4 s and fast drug release. In semisolid extrusion (SSE), 3D printing polyvinylpyrrolidone could be used as a binder. Khaled et al. have prepared of immediate-release paracetamol tablets with drug loading of 80% w/w using 11% w/w PVP K 25 as binder. The obtained tablets were disintegrated in 60 s with complete dissolution in 5 min (Khaled et al. 2018). In binder jet 3D printing technology, PVP K30 was used to produce immediate-release tablets that have a rough structure and visibly porous surface and fast disintegration time (around 90 s) independent of the drug content (Sen et al. 2020; Hong et al. 2021).

2.6 Polycaprolactone (PCL)

Polycaprolactone is a semicrystalline, thermoplastic, biodegradable, and biocompatible polyester produced by cationic or anionic ring-opening polymerization of ϵ -caprolactone at high temperatures (≤ 200 °C), in the presence of a suitable catalyst (Salamone 1998). The structural formula is presented below, in Fig. 4.6.

PCL has good organic solvent solubility and in aqueous media is degraded by hydrolysis of its ester linkages, in physiological conditions (such as in the human body). Due to its very low in vivo degradation rate, high drug permeability, and biocompatibility, it received great attention to be used as an implantable biomaterial for the preparation of long-term implants. The FDA has approved it for specific applications in the medical field, such as drug delivery systems, sutures, or adhesion barriers. Also, lipases and esterases from microorganisms can readily degrade PCL (Ulery et al. 2011; Borandeh et al. 2021; Azad et al. 2020).

Fig. 4.6 Structural formula of polycaprolactone. (Paul et al. 2020)



PCL is commercially available in a variety of molecular weights (MW). Whereas high MW (above 20,000 Da) grades with melting points of about 55–60 °C and glass transition temperatures of 54–60 °C are soft and flexible polymers with an extraordinarily high strain at break, the low MW (below several thousands Da) grades are either viscous liquids or hard waxes. PCL with high MW is considered a good elastic biomaterial due to its low tensile strength (~0.023 GPa) and high elongation at breakage (4700%) (Azad et al. 2020; DURECT Corporation 2022).

The primary use of low MW polycaprolactone is as an additive in polyurethanes, to improve their processing properties and end-use properties such as toughness, flexibility, compression set, and tear strength. PCL impart good resistance to oil, organic solvent, water and chlorine, and polyurethanes. Also, low molecular weight is used as a plasticizer for polyvinyl chloride (PVC) and may be added to other plastics to improve their weather resistance (McKeen 2017, 2021). For pharmaceutical applications, PCL is often copolymerized or blended with other polymers such as polylactic acid (PLA/PLLA/PDLA/PDLLA), poly(lactic-co-glycolic acid) (PLGA), polyethers (PE), polycarbonate (PC) polyethylene oxide (PEO), and polyvinyl alcohol (PVA), to improve erosion and to obtain composites with desired properties (Ulery et al. 2011; Azad et al. 2020; Jiang and Zhang 2017). Mixed with starch allows for obtaining an excellent biodegradable material at a low price (McKeen 2017).

Due to biocompatibility and slow degradation rate, polycaprolactone (PCL) has been widely used in bone tissue engineering for load-bearing applications in the fabrication of scaffolds by 3D printing (Ulery et al. 2011; Yang et al. 2021a; Lee et al. 2015). Other applications based on a slow PCL biodegradation rate are the preparation of implantable drug delivery systems, to deliver the drugs with a controlled-release rate (up to months or years). The desired release profiles might be obtained by choice of the polymer grade, their drug loading, or blending with other biodegradable and biocompatible polymers (Kempin et al. 2017; Holländer et al. 2016). PCL can be blended with a variety of polymers and hydrogels to improve its properties or to introduce new PCL-based composites for the preparation of solid drug dosage forms. The type and grade of the polymer, the presence of a channelling agent and the infill ratio have important influences on the drug loading and drug release profiles from the printlets (Jain et al. 2018; Beck et al. 2017).

2.7 Polyethylene Glycol (PEG)

Polyethylene glycol (PEG), also known under the name of Macrogols, is a linear, hydrophilic polyether of ethylene glycol (ethane-1,2-diol) with a relative molecular weight between 200 and 20,000 Da, for pharmaceutical application. Macrogols are synthesized via anionic polymerization of ethylene oxide and any hydroxyl initiators (Paul et al. 2020; D'souza and Shegokar 2016). The structural formula of PEG, where m represents the average number of oxyethylene groups, is presented below, in Fig. 4.7.

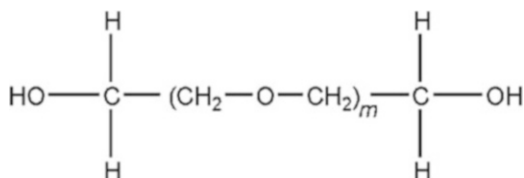
Due to oxyethyl groups, PEGs have good solubility in both water and organic solvents such as ethanol, acetonitrile, dichloromethane, and benzene. They are insoluble in hexane and diethyl ether. The melting point of PEGs depends on their molecular weight. Polyethylene glycol grades with average molecular weight (MW) between 100 and 800 kDa are liquids at ambient temperature; those between 1000 and 2000 kDa are soft solids, while grades with MW above 2000 kDa are hard crystalline solids with melting points of around 63 °C (D'souza and Shegokar 2016).

PEGs are widely used in pharmaceutical formulations, including parenteral, ophthalmic, topical, rectal, and oral preparations, as a solvent, solubilizer, ointment base, permeation enhancer, suppository base, tablet/capsule lubricant, or biodegradable polymeric matrices in controlled-release systems (Ulery et al. 2011; Paul et al. 2020; D'souza and Shegokar 2016).

Accelerated thermal degradation was observed at 195 °C for PEGs MW >20 kDa. High-molecular-weight PEGs (4000, 6000, and 20,000 kDa) have glass transition temperatures at −34.6 °C, −22.7 °C, and −22.37 °C and melting points at 67.7 °C, 58.7 °C, and 51.6 °C, respectively. Low melting points make PEGs widely used in pharmaceutical thermal processing technology like hot-melt extrusion (HME) and fused deposition modeling (FDM), usually blended with other polymers, where they are included as plasticizers, to make the extrusion process easier and to improve the filament flexibility (Pereira et al. 2020; Funk et al. 2022; D'souza and Shegokar 2016). Several studies have reported PEG as a pore former in immediate-release formulations, by improving the entrance of the dissolution medium into the dosage form structure and speeding up the dissolution process (Funk et al. 2022; Fanous et al. 2020).

PEG diacrylate (PEGDA) is a derivative of PEG obtained by adding an acrylic group to the terminal hydroxyl end group of PEG. PEGDA has higher mechanical strength than PEG due to cross-link formation. Moreover, the acrylic groups are photosensitive, aiding its polymerization process where photopolymerization

Fig. 4.7 Structural formula of polyethylene glycol. (Paul et al. 2020)



techniques are used (Azad et al. 2020). PEGDA was used as a cross-linking agent and together with PEG as a plasticizer to fabricate drug-loaded hydrogels via stereolithographic 3D printing (Martinez et al. 2017). Other authors have explored PEG cross-linked polymers (PEGDA and polyethylene glycol dimethacrylate, PEGDMA) as polymers to prepare immediate-release tablets by digital light processing (DLP) 3D printing. Given that tablets remained intact throughout dissolution testing, it is more likely that the dissolution mechanism was controlled by drug diffusion (Stanojević et al. 2021).

2.8 Polyethylene Oxide (PEO)

Polyethylene oxide (PEO), also known under the name of POLYOX or polyoxyethylene, is a nonionic, hydrophilic polymer of ethylene oxide, represented by the formula $(\text{CH}_2\text{CH}_2\text{O})_n$, where n represents the average number of oxyethylene groups (Paul et al. 2020). PEO has similar structure with PEG, the difference being the molecular weight. Polymers with $M_w < 100,000$ Da are usually called PEGs, while polymers with higher molecular weight are named PEOs (Azad et al. 2020).

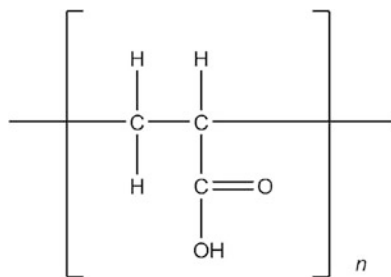
PEO is used in pharmaceutical sector as coating agent, tablet binder, thickening agent, mucoadhesive agent, and matrix-forming polymer in extended-release tablets, including osmotic pump technologies. The existence of a wide range of pharmaceutical-grade PEO with molecular weights between 100,000 and 7,000,000 Da offers a high flexibility in formulation (Paul et al. 2020; Colorcon Inc 2022c). PEO is soluble in water and some organic solvents such as methylene chloride, chloroform, and acetonitrile. It is insoluble in aliphatic hydrocarbons as alcohols and ethylene glycol. It may contain up to 3% of silicon dioxide or suitable antioxidant (Paul et al. 2020; Brady et al. 2017).

High degradation temperature, thermoplastic behavior, and high crystallinity with low melting temperature make PEO suitable feedstock materials for hot-melt extrusion and melt granulation. In 3D printing, PEO can be used as forming material or as an aid (plasticizer) in FDM via hot-melt extrusion (Isreb et al. 2019) and forming material in SLS (Fina et al. 2018b).

2.9 Carbopol

Carbopols, also known under the name of carbomers or polyacrylic acid (PAA), are high-molecular-weight synthetic polymers of acrylic acids cross-linked with allyl sucrose or allyl pentaerythritol or allyl ethers. The molecular weight of Carbopol is estimated theoretically at 7×10^5 to 4×10^9 Da, and the carboxylic acid groups in the molecule are between 56 and 68% w/w calculated on the dry basis (Paul et al. 2020; Brady et al. 2017). Carbomers are repeating units of acrylic acid (as monomers) that have the structural formula shown below, in Fig. 4.8:

Fig. 4.8 Structural formula of acrylic acid monomer unit for Carbopol polymers. (Paul et al. 2020)



Carbopols are well-known for their versatility and ease of use in pharmaceutical sector. They are used in liquid or semisolid formulations as rheology modifiers, emulsifying agents, suspension stabilizers, and emulsion stabilizers and in tablet formulations as tablet binders, controlled-release agents, sustained-release matrix, bioadhesive material, mucoadhesive aids, and bioavailability enhancers. Different pharmaceutical grades of carbomers, with different physical characteristics (especially viscosity characteristics) are available, depending on the manufacturing conditions and the degree of cross-linking. Carbopol 934P is polymerized in benzene and cross-linked with allyl sucrose, and Carbopol 71G, 971P, and 974P are polymerized in ethyl acetate and cross-linked with allyl pentaerythritol. In contact with water, Carbopol absorbs water, hydrates, and swells. Since they are three-dimensional cross-linked microgels, they do not dissolve in water; they merely swell to a remarkable extent if the solution is neutralized. Hydrated in water Carbopol forms an acidic aqueous solution (pH 2–4) that becomes gel-like if the pH is adjusted to alkaline (usually to pH 6–11). If the gels are exposed to ultraviolet light, they rapidly lose viscosity, but this can be minimized by the use of antioxidants. During the neutralization process, the polymer carboxylic groups become ionized and internal repulsion between them forces the polymer chains to stand away and enhance viscosity (Paul et al. 2020; Kaur et al. 2018).

In 3D printing, Carbopol[®] 971P and 974P may be used as suitable for matrix gel preparation in the development of sustained-release tablets via pressure-assisted microsyringe (PAM) technology (Jonathan and Karim 2016; Zidan et al. 2019a, b).

2.10 Polyurethane (PU)

Polyurethanes are a class of elastomers composed of organic units joined by carbamate (*urethane*) links. They are typically produced by the reaction between a *polyol* (soft segment), a *diisocyanate*, and a *chain extender* (hard segments). The hard and soft segment ratio together with the wide variety of monomers available for synthesis allows fabrication of PUs with wide range of physical, mechanical, and chemical properties. Usually they are very flexible and elastic, displaying minimal hysteresis. The biodegradation of PU can be obtained through proper selection of the chemical nature of the soft segment. For example, polyether-polyol is resistant to

biodegradation, while polyester-polyol is readily biodegradable. Classic PUs synthesized from aromatic diisocyanates are not biodegradable, while those synthesized from biodegradable monomers, such as polylactide and polycaprolactone (PCL), can undergo hydrolysis and be used in biomedical applications. In vitro and in vivo studies on biodegradable PU show that they have an acceptable biocompatibility (Ulery et al. 2011; Samavedi et al. 2014; Ibrahim et al. 2017).

Waterborne and organic solvent-free pharmaceutical-grade polyurethanes have been developed for the pharmaceutical applications, especially for the preparation of nanoparticles (Borandeh et al. 2021; Omrani et al. 2016), films (Farzan et al. 2020), hydrogels (Bankoti et al. 2017), and implants (Domínguez-Robles et al. 2020; Bahadur et al. 2018). For 3D printing, thermoplastic polyurethanes (TPUs) have been evaluated as feedstock material in fused deposition modeling and injection modeling. They were found as promising excipients for the manufacturing of high drug-loaded (up to 60%, w/w) personalized dosage forms and for the preparation of tablets with sustained drug release kinetics (Verstraete et al. 2016, 2018; Claeys et al. 2014).

3 Issues and Solutions

Additive manufacturing or 3D printing comprises a list of seven manufacturing technologies, according to ISO/ASTM 52900, of which five have been employed for pharmaceutical applications, as shown in Fig. 4.9. The materials used in these applications are also diverse, but polymers are the most relevant for the applications of these technologies in the manufacturing of pharmaceutical dosage forms.

3.1 *Material Extrusion Techniques*

3.1.1 Fused Deposition Modeling (FDM)

Among the material extrusion techniques, fused deposition modeling (FDM) has been the most used in the pharmaceutical field in recent years, due to the possibility to produce personalized dosage forms and to adapt the drug release profile in function of product geometry. The principle of this technique is the extrusion of a molten material through an extrusion head and subsequent building of the 3D object by deposition of successive material layers on a heated plate and solidification (Wang et al. 2022a; Parulski et al. 2021). The molten material is an extruded polymeric filament, and the deposition of the material is dependent on the drive gears of the equipment but also on the filament properties. Consequently, the polymer blend used to prepare the filament has to be established such as to ensure the drug product quality (active substance content and uniformity, drug release, stability) but also the piston-like function. Thus, the mechanical characteristics of the filament are critical because brittle filaments will be fractured during the FDM

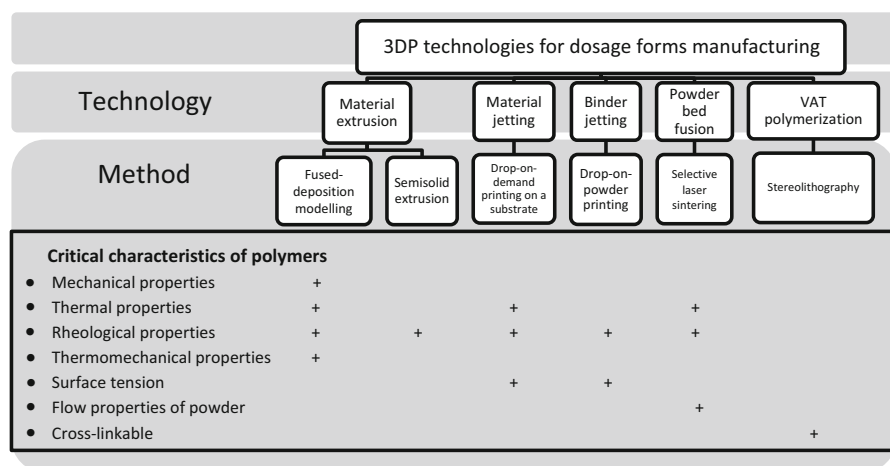


Fig. 4.9 A classification of 3DP technologies with applicability in the manufacturing of pharmaceutical dosage forms and the polymer characteristics relevant for each

printing process, while too flexible ones will undergo deformation (Samaro et al. 2020). It is considered that, for an effective feeding into the 3D printer, the filaments used should show sufficient stiffness, ductility, and toughness (Samaro et al. 2020). Second, the materials used must be thermoplastic, the thermal properties of the filament being decisive for the working conditions (temperature of the printing head, temperature of the build plate) but also for the solidification of the printed dosage form. Because the extrusion temperature must be higher than T_g of the polymer, to have it in the flexible state, and the printing temperature is usually higher, it is recommended to work with polymers having the T_g value as far as possible from the degradation temperature of all components of the mixture. To facilitate the reduction of the working temperature, plasticizers are added in the formulations, which act by decreasing the T_g value of the polymer (Parulski et al. 2021). Third, the material viscosity is important, influencing the extrusion step, but also the consolidation of the printed object (the adhesion between the printed layers, the preservation of the morphology in the cooled state without delamination or breakage) (Ilyés et al. 2019; Spoerk et al. 2019). Thus, if the viscosity of the molten material is too high, the surface of the resulted filament is rough, and the filament could clog the nozzle during printing. However, a high viscosity of the layers enables the printed object to keep its shape, but a low viscosity enables a uniform deposition of the layers during printing (Ilyés et al. 2019).

As described before, the printability of extruded filaments through FDM is mainly influenced by their mechanical suitability, their thermoplastic properties, and their viscosity in the molten state. The printability of the filament is strongly influenced by their composition, not only by the main carrier, represented by a polymer, but also by the active substance and its proportion as well as the presence of additives. Among the additives used, plasticizers are the most common, because they

improve the processing conditions as well as the physical and mechanical characteristics of the filament and of the final product (Crowley et al. 2007). The most used are citrate esters, fatty acid esters, sebacate esters, phthalate esters, glycol derivatives, triacetin, mineral and castor oils, and vitamin E TPGS, but surfactants or even the active substance itself may act as plasticizer (Crowley et al. 2007).

The main issues to overcome for obtaining the ideal printing properties of the filaments are summarized in Table 4.1, along with several examples of solutions proposed by studies published in this field. To evaluate the printability of polymers obtained through FDM, their mechanical characterization is useful, an appropriate stiffness-flexibility-brittleness balance being essential for optimal printability (Azad et al. 2020). For the mechanical characterization of filaments, the tensile test using texture analyzer and the compression tests are probably the most used tools. The tensile test consists in applying a force until filament breaks, followed by the determination of characteristics like brittleness (ultimate tensile strength, strain at breakage), stiffness (Young's modulus), and toughness (the area under the stress-strain curve up to deformation) (Samaro et al. 2020; Nasereddin et al. 2018). It was shown that the results of the tensile test may be used to predict the printability of filaments through FDM (Samaro et al. 2020). Three-point bending test is among the compression tests used, to determine the stress at which plastic to elastic deformation occurs or at which a filament breaks (Govender et al. 2021). The evaluation of thermoplastic properties of the filament is another useful tool for the prediction of FDM printability, as the thermal transitions of the material are taken into account to establish the processing conditions for optimal printability. Usually, combining differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic mechanical analysis (DMA) provides complementary information and allows to establish the optimal thermal processing range for printability (Kissi et al. 2021). Last, determining the viscosity of the molten material can indicate whether a composition is extrudable/printable or not and shear rate test using a capillary rheometer or a rotational rheometer is a tool to predict the changes in viscosity due to shear (Govender et al. 2021; Samaro et al. 2021). The main challenge in establishing the ideal viscosity for printing is that extremely low-viscosity filaments fail to be printed because the mechanical properties, i.e., the piston-like function of the filament is lost (Samaro et al. 2021).

3.1.2 Semisolid Extrusion or Pressure-Assisted Microsyringe Printing

Semisolid extrusion (SSE) is a group of different material extrusion mechanisms, of which pressure-assisted microsyringe printing (PAM) represents the deposition of semisolid formulations (gels, pastes) through non-heated or (optionally) heated nozzles. The extruded material is prepared by mixing polymers and solvents, then is loaded into a syringe, and further is squeezed onto a platform to form the 3D object. The advantage of PAM over FDM is that the material does not need to be melted and extruded at high temperature, so PAM is suitable for thermolabile active substances and a wide range of pharmaceutical polymers, but post-printing drying is

Table 4.1 The main issues to overcome to obtain filaments with suitable printability through FDM and examples of proposed solutions

Objective	Issue	Solution	References
Mechanical suitability of the filament	Filament brittleness causes fractures and block of the printing head	Plasticization of HPMCAS AFFINISOL™ (HPMCAS 716) with PEG 600 and the addition of talc as insoluble structuring agent into the formulation improved printability and thickness consistency of printed layers	Oladeji et al. (2022)
	Too soft filaments bend and get stuck in between the rollers	Kolliphor TPGS improves textural features and makes Kollidon SR and AFFINISOL 15 LV filaments less susceptible to break or shear	Ilyés et al. (2019)
	Filament should possess piston-like function	Plasticization of HPMCAS filaments using polyethylene oxide transformed the non-feedable into feedable filaments	Nasereddin et al. (2018)
Thermoplastic properties	Pharmaceutically approved polymers do not possess adequate thermoplasticity	Addition of glutaric acid using the acid-base supersolubilization principle to haloperidol loaded filaments of Kollidon® VA64 (or its mixtures with AFFINISOL™ 15 cP), improved the printability, and reduced the extrusion and printing temperature	Patel and Serajuddin (2021)
	High extrusion and printing temperatures required due to high T_g of the polymers are harmful for thermosensitive active substances	The addition of PEG, PEO, and Tween 80, to solid dispersions of felodipine with Eudragit EPO or Soluplus overcome the poor printability of the polymers and lowered the processing temperature to prevent the active substance degradation	Alhijaj et al. (2016)
	Decreasing the T_g may alter the mechanical properties of the filament	The addition of water as a temporary plasticizer in a PVA/sorbitol filament (drug-free) enabled lowering the temperatures of extruding (from 170 to 90 °C) and 3D printing (from 210 to 150 °C)	Pereira et al. (2019)
		Surfactants (poloxamer 188, poloxamer 407, and d-alpha tocopheryl polyethylene glycol 1000 succinate) are suitable plasticizers for itraconazole-HPMCAS solid dispersion prepared by hot-melt extrusion, reducing the extrusion temperature (from 170 to 130 °C) and the viscosity	Wei et al. (2020)

Adequate viscosity of the molten material	High viscosity determines poor flow from the nozzle resulting in collapsed structure Low viscosity reduces the piston-like function and prevents proper deposition of the 3D-printed structure	The addition of talc as thermostable filler to PVP improves the flow from the printer, prevents the formation of collapsed structures, and allows the formation of immediate-release tablets (10% drug loading) at 110 °C	Okwuosa et al. (2016)
		Sorbitol enhances the melt extrudability of PVA, through reducing melt viscosity	Wei et al. (2020)
		Printing behavior of EVA filaments depends on the initial viscosity and viscosity variation (max/min ratio) during the frequency sweeps: 18%VA polymer provides a moderate initial viscosity and low max/min ratio, generating filaments with adequate mechanical properties	Samaro et al. (2021)
		The addition of different molecular weight PEG to ciprofloxacin loaded PCL filaments reduces the viscosity, but the influence on adhesion behavior of the layers upon deposition is dependent on PEG's molecular weight	Elbadawi (2019)

EVA ethylene-vinyl acetate copolymers, *HPMCAS* hypromellose acetate succinate, *PCL* polycaprolactone, *PEG* poly(ethylene glycol)s, *PVA* polyvinyl acetate, *PVP* polyvinylpyrrolidone

required (Azad et al. 2020). In this method, the printability of the mixture is mainly influenced by its viscosity, because high-viscosity mixtures will determine nozzle clogging, while a low-viscosity material will not form the 3D structure (Wang et al. 2022a; El Aita et al. 2019).

The success of the printing process in PAM relies on the rheological properties of the material but also on different processing parameters, such as printing pressure, printing speed, nozzle size, and shape, that need to be controlled and optimized for a successful PAM-based printing process (Mohammed et al. 2021). The ideal material used in this technique has to be easily deposited and to provide a stable 3D object. Regarding the composition of the material, the semisolid formulation used is usually a polymeric dispersion in mixtures of water and organic solvent (to allow rapid evaporation after extrusion), in which additives such as powder diluents are used to adjust the rheological properties of the extruded material and the structural integrity of the printed product, disintegrants to ensure immediate release, or plasticizers, for uniform extrusion and improved product appearance. The gel-forming polymers used have viscosity-increasing ability (thickening agents), the most used being Carbopol, HEC, HPMC, and PVP (Govender et al. 2021). An optimization study, aiming to optimize the material and printing parameters by PAM, evaluated several of the most used polymers in this technique (EC, HPMC, PVP, cellulose acetate) as pastes obtained with the help of different solvents (methanol, ethanol, acetone, isopropyl alcohol, dimethyl sulfoxide (DMSO)) or solvent combinations (Mohammed et al. 2021). Besides the polymer and the solvent, a filler (mannitol) and a plasticizer (PEG 6000) were added in the composition of the paste. The issues observed and used as exclusion criteria during formulation optimization were the inability to form a paste, the difficulty to be extruded through the printer nozzle/extrusion inability, the high spreadability at the base, and the inability of layer formation. Based on these issues, cellulose acetate was identified as the ideal polymer, displaying good extrusion behavior, the layer-by-layer deposition ability, and the preservation of the printed structure, while the best solvent mixture was acetone/ethanol/DMSO (1:1:0.4) (Mohammed et al. 2021). When polymer blends are required to get the desired pharmaceutical characteristics of the formulation, their miscibility is an issue to address during formulation development, as well as the impact of the mixing proportion and processing conditions on the rheological behavior, because the ratio between polymers influences the rheology of the material and consequently the printability (Elbadawi et al. 2021; Conceição et al. 2019). Besides the polymeric content, attempts have been made to prepare formulations without organic solvent due to concerns related to their residual content in the product. The presence of organic solvents in the formulation may influence the printability over time, due to the risk of evaporation, thus limiting the use of a stock formulation for several days to reduce the preparation time and to favor the individual dosing (El Aita et al. 2020). The preparation of an organic solvent-free formulation has been successfully performed using a polymer mixture of Kollidon SR[®] and HPMC (Metolose[®] 90SH) and silicon dioxide as supporting matrix agent, only with water as solvent (El Aita et al. 2020).

3.2 *Binder Jetting*

3.2.1 **Drop-on-Powder Printing**

Drop-on-powder (DoP) is a printing method based on bonding the particles of a powder through a binder (printing ink) jetted as droplets over a layer of powder, followed by the lowering of the printing platform, the addition of a new powder sheet on the initial one, and repeating the process until the fabrication of the 3D structure is completed (Mohammed et al. 2020). In this technique, polymers are used as components both of the printing ink and of the powder substrate onto which the droplets are deposited, both playing a role in achieving optimum adhesion (Govender et al. 2021). Although the printing ink may be a solvent, polymeric solutions are used as binders with the purpose of getting stable droplet formation, influenced by the viscosity and surface tension (Wang et al. 2022a; Chou et al. 2021). Regarding the particles of polymer used as powder bed, their flowability is a critical attribute, because each powder layer must be rapidly deposited over the previously solidified powder layer, so particle size, particle size distribution, and powder's density of the polymer will be influential on this (Wang et al. 2022a).

Besides the specific characteristics of each individual component involved in binder jetting, i.e., binder solution and powder substrate, the interaction between them is important, this interaction being evaluated through wettability and bindability of the powder (Sen et al. 2021).

In this method, the printability of the binder solution is defined as its ability to form similar volume of droplets on each occurrence, and it can be evaluated using Ohnesorge number, a dimensionless number which depends on surface tension, density, and viscosity of the solutions (Sen et al. 2020). To formulate a binder solution with ideal printability, the Ohnesorge number has to be between 0.1 and 1, the solution being too viscous to be dispersed from the printhead or, on the contrary, determining the formation of unwanted satellite droplets, if the values are out of this range. To achieve this goal, several formulation strategies are possible. First of all, water alone is not a suitable solvent, due to its high surface tension, but water-ethanol mixtures, ethanol-acetone-water, as well as nonaqueous solvents (chloroform)/mixtures (ethanol-acetone) are used (Jonathan and Karim 2016). To optimize the viscosity and the binding capacity of the ink, polymers are used, PVP, PEG, and HPMC being the most researched. Despite the benefits of adding polymers in the solution, an issue associated with the use of polymeric solutions is nozzle clogging phenomenon, the risk of which increases with the formulation complexity (e.g., when the active substance is incorporated in the same solution) (Kreft et al. 2022; Wang et al. 2022b). To overcome this risk, the binder can be used as a component of the powder layer (Wang et al. 2022b). PVP is usually utilized as solid binder, but HPC has also been reported as suitable for this purpose (Hsiao et al. 2018). Regarding the characteristics of the powder layer, the wettability is favored by its hydrophilic components but hampered by the presence of hydrophobic active substances. To counteract this issue, spray-drying was used to embed hydrophobic

active substance crystals within hydrophilic matrices made of PVP and lactose, and this led to enhanced printability with water-based binders (Kozakiewicz-Latała et al. 2022).

3.3 *Material Jetting*

3.3.1 **Drop-on-Demand Printing on a Substrate**

DoD printing is based on the ejection of droplets from the nozzles created by a pressure pulse, i.e., thermal, piezoelectric, electrostatic, or acoustic actuation. The generated droplets have sizes between 10 and 50 μm and a volume of 1–70 pL, the printing resolution and accuracy being high but dependent on liquid formulation and the characteristics of the nozzle (Chou et al. 2021). This technology is suitable for printing of a variety of pharmaceutical formulations, such as solutions, emulsions, suspensions, or even dispersions of polymeric or lipid nanoparticles (Elele et al. 2020). The formulation of the liquid may be optimized in terms of surface tension and viscosity, so polymers may be added in the formulation to adjust these characteristics. Thus, the surface tension of the liquid must be low enough to allow droplet formation, while during deposition, the surface tension has to be sufficiently high to prevent leaking from the nozzle. Regarding the viscosity of the liquid, it has to be low enough that the fluid can be jetted but sufficiently high to prevent early ejection from the printhead and the production of satellite droplets (Alomari et al. 2015). Thus, optimal ranges have been established for both surface tension and viscosity, i.e., between 30 and 70 mN/m and 2 and 20 mPas, respectively (Govender et al. 2021).

The formulation of the jetted solution used in this technique is the main challenge because it contains the active substance, so reliable jetting and uniform drop formation are mandatory for product quality. Additionally, the solvent used and drying rate after deposition will influence the state of the active substance in the final product and, consequently, the bioavailability (Hsiao et al. 2018). Another challenge is to adjust the physicochemical characteristics of the solution to the print head requirements, as different principles are applied. The most used are thermal printing, involving the use of heat to force out the fluid from the nozzle, and piezoelectric printing, which uses a piezoelectric transducer for drop formation and allows working at room temperature or even in cold environment. Aqueous solutions are more suitable for the thermal method, while organic solutions are appropriate for the other method. The viscosity range for optimal deposition of the jetted solution has to be established for each method used, the viscosity being considered as the most critical formulation parameter to affect deposition (Buanz et al. 2011). Because the viscosity has to be relatively low, the most used viscosity-increasing agents are glycols (glycerol, propylene glycol), but polymers are also used for the same purpose (PEG, HPMC, HEC, HPC, starch) (Govender et al. 2021). Although PEG is the most used polymer for ink formulation, its suitability depends on the substrate. For

example, when HPMC film is used as substrate, PEG 400 causes insufficient drying due to low vapor pressure and limited penetration into the substrate (Kiefer and Breitzkreutz 2020). To solve the dispersion problem of viscous liquids but also the difficulty to print water-insoluble substances, a group of authors proposed the use of an aqueous suspension of active substance nanoparticles obtained through wet stirred media milling (Elele et al. 2020). A more recent approach is to print a viscous polymer-active substance solution to fabricate films in a single step, without the need of a polymeric substrate, using a piezoelectric micro-dispensing system. Contrary to the usual method, this technology allows dispensing high-viscosity materials (15% HPMC solution), a high viscosity of the ink being required to enable the formation of a continuous film (Tam et al. 2021). Tablets without edible substrate being part of the tablet were also printed, using a water-based ink containing PVP (Cader et al. 2019). The substrate-less approach is useful for DoD applications in dosage form manufacturing, because many studies are performed using substrates which are not suitable for this purpose (polytetrafluoroethylene films, paper, etc.). Regarding the pharmaceutically acceptable supports onto which the droplets are deposited, they vary from polymeric films to porous materials, such as dry foams or tablets (Edinger et al. 2017). It was shown that polymer type/grade, film thickness, and porosity influence the drug release profile but also the printing success.

3.4 Powder Bed Fusion

3.4.1 Selective Laser Sintering

The printing technologies based on powder bed fusion use a heat source to melt or fuse materials according to a digital design and to create 3D objects. In selective laser sintering (SLS), the energy source is a laser beam, which heats a powder above its melting point or glass transition temperature (Mohammed et al. 2020).

The characteristics of the polymers which influence the printability through SLD are the ability to absorb energy at the laser wavelength, their thermoplastic properties, and the rheological behavior of the powder as well as of the melt (Wang et al. 2022a; Rahman et al. 2018). Colorants as Candurin[®] NXT Ruby Red, Candurin[®] gold sheen, and tartrazine, have been proposed as additives for sintering, due to their ability to enhance the absorption of energy from the laser beam (Hamed et al. 2021; Yang et al. 2021b). For example, sintering of Kollicoat IR (Kollicoat), Eudragit L100-55 (Eudragit), HPMC E55, or Kollidon VA64 mixed with paracetamol was not possible in variable temperature and laser scanning speed conditions, due to the lack of interaction between the laser beam and the powder, but the addition of 3% Candurin[®] gold sheen in the mixtures allowed the material sintering and formation of porous structures, suitable as oral products (Fina et al. 2017, 2018a). Because polymers used in SLS have similar requirements as those used in FDM, the same materials are used in both techniques, i.e., blends of active substances with thermoplastic polymers (polymethacrylates, PVA, PEG, PEO, PVA-peg graft copolymers)

(Funk et al. 2022). However, while polymers are completely molten in FDM, leading to denser structures, in SLS, particle size distribution and modulation of laser scan speed influence the sintering effect and the formation of denser/more porous structures (Funk et al. 2022; Fina et al. 2018a). Additionally, for SLS, flow behavior of the powder particles is important, to ensure uniform powder spreading and layer formation during the process (Averardi et al. 2020). To improve the flow behavior, besides controlling the size and shape of the particles, the addition of additives improving powder flow, such as talc, silica, calcium, and magnesium silicates, has been proposed (Ligon et al. 2017; Hamed et al. 2021). Regarding particle size, the size range between 58 and 180 μm is considered ideal for successful sintering, while narrow particle size distribution ensures even absorption of energy (Leong et al. 2006; Awad et al. 2020). Grinding and sieving are recommended to achieve the desired particle fraction. Using polycaprolactone (PCL) and poly(–L) lactic acid (PLLA) with controlled particles size, (100 μm and 125 μm , respectively), porous microstructures with specific porosity were fabricated, as a mean to achieve a zero-order drug release kinetics, by varying the most influencing process parameters (laser power intensity and laser scan speed) (Leong et al. 2006). It was shown that packing of the powder bed has to be consistent from one layer to another for reproducible printing, because packing influences the porosity but also the thermal behavior of the powder (Averardi et al. 2020). The polymer nature also influences the thermal behavior, because sintering of polymers occurs mainly due to partial or complete melting of powder particles, which depends on the semicrystalline or amorphous nature of the polymer, the molecular structure, and molecular weight, so the adequate polymer sort has to be selected through a systematic analysis, using tools as differential scanning calorimetry and thermomechanical analysis, rheology, and density evaluation (Ligon et al. 2017).

3.5 VAT Polymerization

3.5.1 Stereolithography

VAT polymerization involves 3D printing through layer-by-layer solidification of a photosensitive polymer, induced by UV light. There are several VAT polymerization techniques, stereolithography (SLA) being the most researched for drug delivery applications. The starting materials used in this technology are monomers or oligomers (photoresins) in liquid state, which polymerize/cure when exposed to UV energy, in the presence of a photoinitiator (PI). By polymerization, the cross-linked polymer traps in the polymeric network all the other components of the initial blend, including the active substance. In SLA, the main challenge to formulate the product is to find a suitable photosensitive polymer, because the number of photocrosslinkable polymers which are generally recognized as safe is reduced (Rahman et al. 2018). Among them, some examples are Poly(ethylene glycol) diacrylate (PEGDA), poly(propylene fumarate)/diethyl fumarate (PPF/DEF), poly

(ethylene glycol) dimethacrylate (PEGDMA), and poly(2-hydroxyethyl methacrylate) (pHEMA), with applications in printing of tablets, hydrogels, and polypills (Martinez et al. 2017; Wang et al. 2016; Robles-Martinez et al. 2019; Healy et al. 2019; Karakurt et al. 2020). The main issues regarding SLA are the safety of photocrosslinkable polymers and the need of at least one PI, which may also pose toxicity problems. To date, riboflavin has been proposed as nontoxic PI, used in SLA fabrication of a controlled-release PEGDA hydrogel (Martinez et al. 2017). In terms of processability, the resins are highly viscous at room temperature due to their high molecular weight, and the viscosity is further increased by the presence of solutes (Huang et al. 2022). A possible solution to process high-viscosity polymers is to work at high temperature, which improves the flowability, the process being called thermally assisted stereolithography (Dall et al. 2020). It has been shown that working at high temperatures (i.e., 70 °C) allows the incorporation of high solute loadings (up to 30% PEG 4000 in PEGDA), and consequently printability and biocompatibility are improved with PEG concentration (Huang et al. 2022). Thus, despite the demonstrated potential of this technology for printing drug delivery systems, the development of new and safer excipients as well as of new working conditions to allow the reduction of the concentration of toxic excipients is needed as possible solutions to convert it into one suitable for fabrication of medicines for human use.

4 Conclusions

A lot of polymers may be suitable for manufacturing of dosage forms via 3D printing technology. The main advantage of using pharmaceutical-grade polymers is that they are already approved for human use. Often, blending or loading polymers with drug substances determines the change of their primary properties that make them suitable for 3D printing, and proper solutions are needed to overcome this. Regarding the issues associated with the use of polymers in 3DP technologies, it can be stated that they are method-dependent, but many of them are common to several technologies that apply similar working principles or similar starting materials, and, consequently, the proposed solutions may be the same as well. Thus, the critical polymer/material characteristics are: thermoplasticity for methods involving phase transition/melting (FDM, SLS), rheological behavior for extrusion-based techniques (FDM, PAM), viscosity and surface tension for solvent-based methods (DoP, DoD), and powder flow for methods using powder substrates (SLS, DoP).

MCQs

1. The feedstock materials used for pharmaceutical applications of 3D printing:
 - A. Are designed especially for 3D printing
 - B. Are polymers alone or in blends with other pharmaceutical excipients
 - C. Have been traditionally used in pharmaceutical field for other applications

- D. Must have a good thermostability for material extrusion techniques
 - E. Must have a good thermostability for VAT polymerization technologies
2. The use of polyvinyl alcohol (PVA) in hot-melt extrusion (HME) and fused deposition modeling (FDM) 3D printing is based on its following characteristics:
- A. Thermostability
 - B. High mechanical strength and elasticity
 - C. Ability to load high proportions of active substances through the soaking method
 - D. Ability to load high proportions of active substances by extruding a mixture of PVA and active substance
 - E. Possibility to tailor the drug release profile
3. Cellulose polymers used for pharmaceutical applications of 3D printing:
- A. Microcrystalline cellulose is adequate for fusion-based methods due to its very high melting point (around 450 °C)
 - B. Ethyl cellulose (EC) has high thermostability and adequate thermoplastic properties
 - C. Hydroxypropyl cellulose (HPC) may be processed at low (120 °C) or high (200 °C) temperature, depending on the molecular weight
 - D. Hydroxypropyl methylcellulose (HPMC) has been used to prepare 3D-printed solid dosage forms by SLS, FDM, or inkjet printing
 - E. Hydroxypropyl methylcellulose acetate succinate (HPMC-AS) offers the possibility to obtain gastro-resistant tablets directly through FDM 3D printing
4. The critical characteristics of polymers used in fused-deposition modeling are:
- A. Mechanical properties: filament should be brittle
 - B. Thermal properties: low extrusion and printing temperatures are desirable
 - C. Rheological properties: high viscosity improves the flow from the nozzle
 - D. Thermoplastic properties: improved by the addition of plasticizers
 - E. Mechanical properties: filament should possess piston-like function
5. The main issues of the polymers used in pharmaceutical applications of 3D printing:
- A. Pharmaceutically approved polymers do not possess adequate thermoplasticity (for FDM-3DP)
 - B. The semisolid dispersions of polymers are highly spreadable and do not form stable 3D structures (in PAM)
 - C. Polymeric solutions used as binders cause nozzle clogging (for FDM-3DP)
 - D. Poor ability to absorb energy at the laser wavelength (for SLS)
 - E. The reduced number of photocrosslinkable polymers which are generally recognized as safe (for VAT polymerization)

6. The ideal characteristics of materials used in pharmaceutical applications of 3D printing technologies:
 - A. For SLS: excellent powder flow of powder polymer, ability to absorb energy at the laser wavelength
 - B. For PAM: easy deposition and stability of the printed structure
 - C. For DoP: stable droplet formation for the binder solution, rapid, and uniform deposition of each powder layer
 - D. For FDM-3DP: high T_g , to allow high extrusion and printing temperatures
 - E. For DoD: very high viscosity and surface tension

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Chapter 5

Quality by Design (QbD) Approach for Individualized Products Based on Additive Manufacturing



Jukka Rantanen

Abstract Manufacturing of pharmaceuticals has not traditionally been in the forefront of implementing recent development within engineering sciences. The most visible part of pharmaceutical sciences is often the search of new active substances and commercial driver is the identification of a “blockbuster” molecule. At the same time, the classical production of pharmaceuticals has been driven by *Quality by Testing* thinking and engineering solutions dating back even to patented inventions from 1840s (tablet). Pharmaceutical quality systems have been heavily based on testing the quality into the end-product and intensive documentation of all the steps of the production cycle. However, the increasing pressure on cost of medication for society and an obvious need for more individualized products challenge all this. The way of thinking about quality has not been fostering innovative manufacturing solutions paving the way toward more efficient production systems and tailor-made therapies. All this has been changing rapidly during the past decade and the innovative pharmaceutical manufacturing sciences have matured into an integrated part of broader pharmaceutical sciences.

Keywords Artificial intelligence (AI) · Biopharmaceutics risk assessment roadmap (BioRAM) · Continuous manufacturing · Data sciences · Design of experiments (DoE) · Digital therapeutics (DTx) · Failure mode and effects analysis (FMEA) · Ishikawa diagram · Machine learning · Near-infrared (NIR) spectroscopy · Process simulation · Quality by Design · Process analytical technologies (PAT) · Raman spectroscopy · Real-time release testing (RTRT) · Relative risk ranking (RRR) · Risk assessment · Risk priority number (RPN) · Target product profile (TPP)

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1 Perspective to Manufacturing Sciences

Manufacturing of pharmaceuticals has not traditionally been in the forefront of implementing recent development within engineering sciences. The most visible part of pharmaceutical sciences is often the search of new active substances and commercial driver is the identification of a “blockbuster” molecule. At the same time, the classical production of pharmaceuticals has been driven by *Quality by Testing* thinking and engineering solutions dating back even to patented inventions from 1840s (tablet). Pharmaceutical quality systems have been heavily based on testing the quality into the end-product and intensive documentation of all the steps of the production cycle. However, the increasing pressure on cost of medication for society and an obvious need for more individualized products challenge all this. The way of thinking about quality has not been fostering innovative manufacturing solutions paving the way toward more efficient production systems and tailor-made therapies. However, all this has been changing rapidly during the past decade and the innovative pharmaceutical manufacturing sciences have matured into an integrated part of broader pharmaceutical sciences.

One example of this development is the recent implementation of *Quality by Design* (QbD) concept in the pharmaceutical field. QbD is a regulatory framework for structured and risk-based development of a pharmaceutical product. The framework for QbD is based on quality systems well-established in other industries, e.g., Japanese car industry. This thinking has been pioneered by Juran already several decades ago, and it has been implemented into pharmaceutical systems during this millennium. The US Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH) have been operative in implementing a regulatory framework for these principles in the pharmaceutical business area. The existing ICH quality guidelines provide an overview of different elements of QbD. Yu et al. have presented this approach in the context of classical powder-based product design (Yu et al. 2014).

This chapter is not aiming to introduce the full regulatory framework but rather aiming to walk through the practical considerations when implementing QbD into the innovative product design based on additive manufacturing (AM). The term QbD can be referring to activities at different levels; however, it is important to clearly define the goal of the development project when working with pharmaceutical products (Fig. 5.1). A starting point in this work, *target product profile* (TPP), is referring to a broad multivariate set of characteristics defining the desired product. The TPP is a fundament of the following phases of QbD-based development process. AM allows for more degrees of freedom in designing the product structure, and it is critical in the beginning of this design process to clearly define the desired characteristics and performance of the envisioned product. After defining the TPP, the first level of QbD approach (*exploratory investigation*) can start – in this step, the experimental work is needed to learn more about the system behavior. In the context of AM-based processing, this can refer to experimental work with the materials and decision on which AM technique to choose. The TPP defines clearly, how the

Fig. 5.1 An overview of Quality by Design thinking as a part of pharmaceutical product design



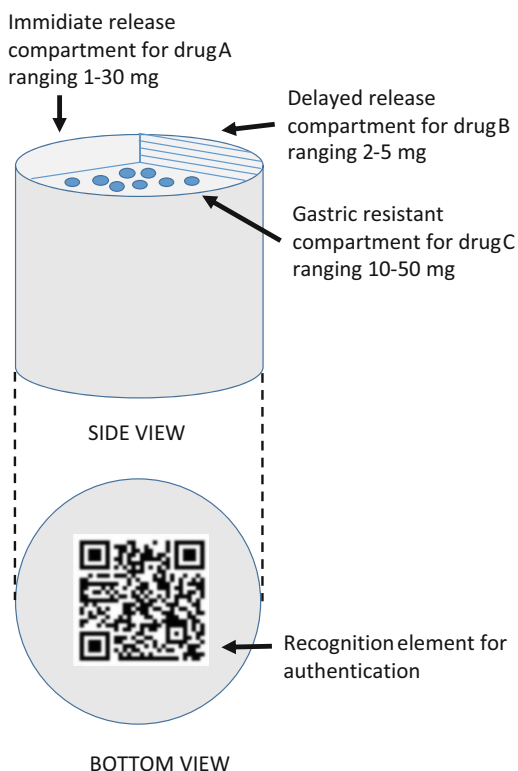
product is expected to perform and in the *exploratory investigation* phase, the decision on the development strategy is made. All this experimental work is providing a basis for understanding the more detailed system behavior (*mechanistic understanding*). Based on both the structured experimental work and mechanistic understanding of the AM product, a *control strategy* can be constructed. During the whole QbD-based development cycle, it is critical to consider the use of process analytical technology (PAT) tools. Moving the analytics toward production environment and implementation of handheld analytical solutions opens up totally new possibilities for quality control of individualized, manufacturing-on-demand production.

This type of QbD- and PAT-based approach is well defined for classical powder-based oral solid dosage forms and related production systems, and an interested reader is encouraged to read more from the existing textbooks, such as *Aulton's Pharmaceuticals*, 6th edition. This book chapter is aiming to provide an overview of QbD-based approach for designing and manufacturing AM-based pharmaceutical products with individualized features. The following chapters will follow the structure as presented in Fig. 5.1.

2 Identifying the Target Product Profile (TPP)

All structured product design and engineering starts by careful planning and constructing a *target product profile*. Products should be designed with the end user in focus, and logically, with pharmaceutical products the end-user is the patient. AM is a manufacturing solution that gives the pharmaceutical scientist totally new possibilities. It allows for more freedom in designing new functionalities into the product, but it is important to have a clear goal and well-structured target product profile from the very beginning. The final product can be designed to release the active substance in an innovative manner, it can contain several active substances,

Fig. 5.2 An example of multicompartamental drug delivery system with three compartments for drugs A, B, and C together with a recognition element at the bottom of the product



and the product can be connected to a broader digital health environment – all this opens up totally new possibilities for innovative drug therapy. A technical drawing of such product is illustrated in Fig. 5.2, introducing an idea of delivering three different drugs with three different formulation strategies in a single-dosage unit. This imaginary example of drug delivery system contains also recognition elements for authentication of this dosage unit (Raijada et al. 2021). Authentication of products is important when designing individualized products for tailor-made therapies and especially when individualized therapies are designed to be supported by digital therapeutics (DTx). These DTx solutions are, e.g., smartphone applications containing a digital interface for patient to support the treatment. Connecting a product to the digital environment should be based on a cybersecure solution based on robust recognition elements in the product.

Biopharmaceutics risk assessment roadmap (BioRAM) has been suggested as an approach for application of systems thinking to patient focused decision-making in the drug development process (Selen et al. 2020). Here, clearly defined patient needs and estimated dose for the desired clinical effect are connected to a formulation strategy, physicochemical properties of the active substance(s), robust in vitro product testing methods, and commercial scale production. Innovative product structures based on AM technologies allow for rethinking the whole drug delivery solution,

including the “polypill” concept (many drug compounds in a same dosage unit), compartmentalized drug delivery systems, and adjustment of the individual drug release profiles. With that in mind, it is important to carefully plan the in vitro test setup. A classical in vitro test might not always be suitable for an individualized pharmaceutical product.

AM-based production methods have been advocated as a potential solution for mass customization of products allowing for more individualized therapies (Govender et al. 2020). This development is underpinning the importance of including the patient and patient population into the design process. Pharmacogenetic information (e.g., differences in receptor level responses, drug uptake to cell, drug plasma protein binding, metabolism) connected with other health data elements, such as patient demographics provides a possibility to design individualized products. The use of all this rich health data can be used to estimate the variety of different doses and even individualized release mechanisms that need to be produced for the whole population. AM-based processing allows for a different level of freedom in the design of the product, and the design process should start with a clear definition of the target product characteristics. According to the QbD principles, a TPP is a starting point for the product design. When designing an individualized product with connection to digital therapeutics, the TPP contains additional elements (Table 5.1) in contrast with, e.g., a more classical compacted tablet product. It is important to collect all the design elements into TPP in order to keep the focus in the design process and to ease the communication between different participants in the process. Stegemann et al. have constructed a roadmap for patient-centric drug product design as a multidisciplinary approach, with a goal of achieving better usability, adherence, and acceptance of the drug by patients via early integration of patients aspects into the development matrix (Stegemann et al. 2022).

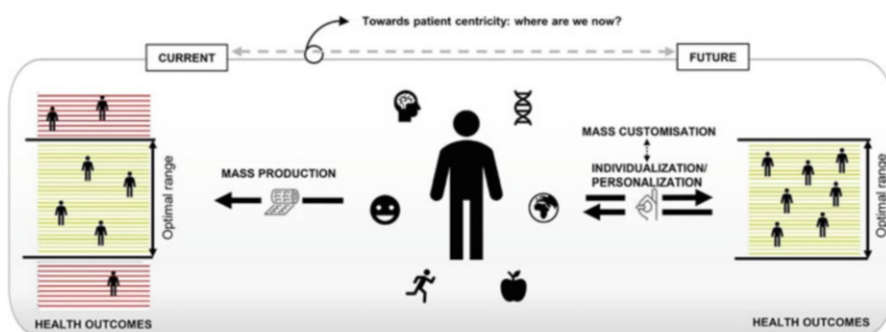
An important element to consider is the identification of technical solutions allowing for mass customization of the product. This is a key for utilizing a full potential of the personalized health data (Rajjada et al. 2021). AM technologies allow for adjusting the product according to the patient needs, but it is also important to include considerations of integration to health data and the whole supply chain model into the product design (Fig. 5.3). Individualized products based on manufacturing-on-demand require different supply chain model when contrasted with the existing mass-produced, “one-size-fits-all” products. In a mass customization scenario, the relevance of PAT and innovative control strategies is increasing.

3 Exploratory Phase: Risk-Based Product Design and Development

After clearly defining the goal of the product design and constructing the TPP according to the patient needs, the decision on the method of manufacturing is needed. All the potential AM techniques are introduced in this book, so there is no

Table 5.1 An example of target product profile (TPP) for an AM-based individualized product

Target Product Profile element	Target	Justification
Dosage form	Solid dosage form	Easy oral administration for the target patient population
Dosage design	Easily swallowable, fast drug release of the customizable dose, taste masking	Patient preference
Route of administration	Oral	Ideal for the patient population
Number of active substances	If needed, construct a 'polypill'	The whole treatment of a patient needs to be considered
Dosage strength range	Customizable between desired range	Highly varying dose based on patient Treatment may require dose tapering
Pharmacokinetics	Release mechanism can be adjusted according to the patient needs	Drug absorption can be affected by patient characteristics
Pharmacogenetics	Dose needs to be individualized based on pharmacogenetic input	Cytochrome P450 (CYP450) drug-metabolizing enzyme related variation in metabolism
Stability	to be defined; e.g., 1-month for an amorphous product can be an attractive alternative	Shorter shelf-life justified because individualized and connectable dosage units (manufacturing-on-demand)
Drug product quality attributes	Pharmacopoeial requirements	Matching with the requirements for the given dosage form
Container system	Suitable container closure system to achieve the target shelf-life and ensure product integrity during shipping	Individualized dosage units can be shipped to patient easily, and contain recognition element both at container and dosage unit level
Sustainability	Additive selection (polymer carrier, plasticizer, filler etc.) includes sustainability consideration	The ultimate production and supply chain solution should be sustainable
Recognition	Each dosage unit should contain unique recognition element for authentication	Individualized treatment needed for each patient
Digital therapeutics aspect	Each dosage unit should be connected to smartphone application	Therapy supported by smartphone application

**Fig. 5.3** Contrasting the current mass production of pharmaceuticals with mass customization model for personalized medicine. (Reprinted from Govender et al. 2020 with a permission from Elsevier)

need to repeat it here. The “exploratory phase” in this chapter is referring to experimental work based on careful risk assessment. The structured utilization of risk assessment tools as a part of broader risk management strategy is a key for successful QbD approach. Risk management is referring to a process aiming to identify, evaluate, and prioritize related to a given system. Risk management is commonly used in many different areas than pharmaceuticals, including finance, insurance, and other areas of production technologies. It is important to consider all potential risk scenarios related to the case under investigation, which is underpinning the importance of collecting a multidisciplinary team for the risk assessment. In the case of individualized pharmaceuticals and products with features as presented in Table 5.1 and Fig. 5.2, it is critical to include different type of expertise in the risk assessment process. Expertise based on pure engineering knowledge is not enough, and further competences covering, e.g., clinical needs, biological aspects related to drug release, patient preferences, data sciences, quality control are needed in this team. It is important to include this input for decision of the AM method capable of fulfilling the desired TPP.

Risk Assessment

Risk assessment tools can be divided into *qualitative* and *quantitative* methods. There is a common misconception that there is only one “golden standard” method for doing risk assessment. It is important to keep in mind that one single method is not always suitable for all possible cases and depending on the stage of the product design, different methods will be needed. It is not logical to start with a full quantitative risk assessment in a very early phase of designing an individualized product based on AM methods. A better approach is to use the qualitative tools in the early development and move toward quantitative methods in the later phase of development. Commonly used qualitative method is *Ishikawa* diagram, or “fishbone” diagram. The *Ishikawa* diagram is aiming to provide a high-level overview to the system and help in communication during the development process. An example (Wang et al. 2022) of the use of *Ishikawa* diagram for exploring the factors affecting the outcome of binder jetting 3D printing is presented (Fig. 5.4). The *Ishikawa* diagram can also contain “semiquantitative” elements, such as colors indicating the most critical factors.

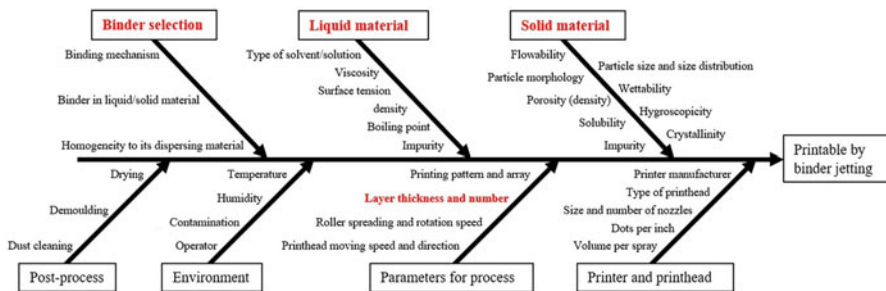


Fig. 5.4 Qualitative risk assessment of binder jetting 3D printing with *Ishikawa* diagram. (Reprinted from Wang et al. 2022 with a permission from Elsevier)

Table 5.2 Relative risk ranking (RRR) for AM-based individualized compartmental multi-drug product with inkjet-printed recognition elements

Drug Product CQAs	Materials; including active substance (API) and excipients					
	Particle size	Solid form selection	Hygroscopicity	Ink selection	Physical stability	Chemical stability
Assay						
Product shape						
Drug release						
Connectability to DTx (digital therapeutics)						

 Acceptable risk level. No further action needed
 Risk is acceptable, but further risk reduction is needed
 Risk is not acceptable. Investigation and risk reduction action needed

This type of qualitative risk assessment can be partially performed based on a literature search, but it is also important to prepare the first prototype products and get some practical insight into the product design. It is critical that the risk assessment team has hands-on expertise with the AM method in order to construct more detailed risk assessment when proceeding toward structured experimental design and finally optimization of the final product. The quantitative, or “semiquantitative” risk assessment tools can be utilized when there is a basic understanding of the system behavior and when moving toward commercial scale production. Relative risk ranking (RRR) is a commonly utilized “semiquantitative” approach, where a design matrix is constructed aiming to visualize how different material or process factors can affect the final product. Typically, visual color-coding is used in to indicate the potential high-risk scenarios, e.g., with a red color (Table 5.2). In this example, RRR is utilized to visualize the potential risk elements related to material properties when designing an AM-based individualized compartmental multidrug product with inkjet-printed recognition elements (Fig. 5.2). Here, the particle size of different drug compounds can affect the drug release from each compartment, as well as the product shape can be a high-risk design element. In this example, particle size is affecting the dissolution rate, and the selected drug compounds have a potential for degradation if they are located close to each other in the dosage unit. Design process should focus on optimizing and stabilizing the particle size, as well as designing a compartmental product allowing for spatial separation of the drug compounds from each other. This product has also recognition elements based on inkjet-printed recognition elements, which leads to a risk scenario at a critical level when designing the ink composition and the matrix structure.

An example of quantitative risk assessment methods is failure mode and effects analysis (FMEA). The quantitative risk assessment methods require a numeric ranking (scale) of three key aspects: probability (P), severity (S), and detection (D). All these three aspects are quite intuitive and straightforward. The FMEA is

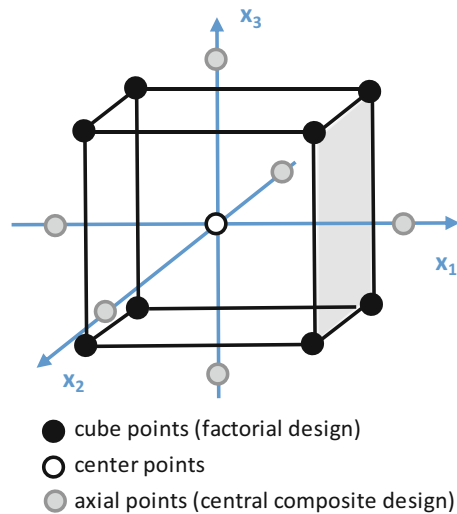
aiming to estimate probability (likelihood of the failure occurring), severity (the consequences of a failure mode), and detection (detectability of the failure mode) on a numeric scale from, e.g., 1 to 5. Typically a high number is referring to a negative scenario, such as high ranking of severity at a level of 5 is referring to a potential death of the patient. During the FMEA process, the risk assessment team is evaluating the whole production cycle and each processing step and evaluating the P, S, and D value for this specific step of production. After this, a risk priority number (RPN) is calculated for each step by simply multiplying the P, S, and D values ($RPN = P \times S \times D$). Finally, all the steps of processing have an individual RPN, and these steps can be organized in the rank order. This list can be used to prioritize the activities in a strategy for risk reduction and risk control.

Design of Experiments (DoE)

After this overview of a given product is achieved by careful construction of TPP and performing the risk assessment at a desired level, the next logical step is to identify experimentally the right operating conditions. Design of experiments (DoE) is a key for a successful experimental work, where the focus is to identify how the predetermined factors (such as, particle size of the API and temperature of the nozzle in a *fused deposition modeling* FDM printer) are affecting the selected response (such as drug release). There are a variety of DoE techniques available that can be utilized for exploring totally new products and processes, optimizing the existing ones and testing the robustness of an existing production system. A short introduction to different DoE methods is introduced here, but a more thorough overview can be found from dedicated textbooks (e.g., Montgomery textbook “*Design and Analysis of Experiments*”) or material from a selected software provider.

The factors that are included in the DoE should be selected after performing a risk analysis, in order to optimize the time and money used for the experimental work. The levels of factors (such as particle size and temperature) are investigated at different levels, e.g., at a low and high level. It is important to have a basic knowledge about the materials and the selected process, so that the level of these factors can be selected at realistic levels. When exploring an AM-based production, there is relatively little prior literature available. This can lead into a high number of factors that should be investigated experimentally. Typical starting point for the experimental work is *factorial design*, e.g., two factors investigated at two levels or two factors at three levels. This leads to 2^2 or 3^2 experiments, i.e., to four experiments with two levels to nine experiments with three levels. This can be generalized and the number of experiments can be expressed as n^k (n number of levels and k number of factors). It is quite clear that a system analysis with full factorial design is not possible and when investigating five factors at two levels, a total of 32 experiments are needed ($2^5 = 32$). This is underpinning the importance of considering *fractional factorial design* in the early phase of product design. In a fractional factorial design, parts of the experimental point are systematically left out in order to reduce the number of experiments. For the earlier example with five factors, a design with 2^{5-1} design would lead to only half of the experiments (16 experimental points instead of 32). When moving toward system optimization and exploring

Fig. 5.5 DoE example with three factors highlighting factorial design at two levels ($2^3 =$ eight experimental points, closed black symbols), center points (open symbols), and the addition of six points to form a central composite design



nonlinear relationships of factors, more than two levels of each factor need to be explored. This can be performed using central composite design, where a defined number of experimental points are added to the DoE. An example of central composite design together with a classical factorial design is presented in Fig. 5.5.

It is also a recommended practice to include a center point, where all factors have a value in the middle of the low and high value of the given factor (Fig. 5.5). In order to make the work easier to communicate and calculations more straightforward, the coded values -1 , $+1$, and 0 can be used for the low, high, and center point values, respectively. It is also a good practice to repeat the center point experiment few times, typically three times. After performing the experimental work, the results are fitted using polynomial fitting to identify the factors of importance. This mathematical model can be also used for visualizing the results using surface response methodologies.

Exploratory Data Sciences

Pharmaceutical area is experiment-driven, and designing a pharmaceutical product involves knowledge-based interpretation of experimental results. Mimicking this process and extracting the “formulation experience” from a skilled formulation scientist is difficult. This is further complicated by experience-based nature of this process where even part of the information can be based on visual evaluation and ranking of alternative formulations. Recent development of analytical instruments and imaging methods has increased exponentially the amount of the data available for a formulation scientist. This combined with increasing computer power and performance of algorithms allows for computational product design. Machine learning (ML) is a group of artificial intelligence (AI) algorithms, where a computational method (algorithm) is trained based on a body of data. In the field of AM process and product design, machine learning has been utilized for designing an AI/ML-based

tool for combining materials data and published formulation knowledge for predicting the process operation parameters (Elbadawi et al. 2020). When performing this type of data mining approach, there are three critical steps:

- (i) Data acquisition and cleaning
- (ii) Evaluation of different models and selection of optimal modeling approach
- (iii) Model interpretation

The importance of data sciences will inevitably increase in the future and it is crucial to include the basic programming skills into the toolbox of every pharmaceutical scientist.

4 Mechanistic Understanding

The term *process understanding* is commonly used expression in the context of Quality by Design approach. It is important to aim for a mechanistic understanding of system behavior when aiming for robust production of pharmaceutical products. This can be achieved by careful investigation of the system of interest leading to mechanistic understanding of the critical physical and chemical phenomena occurring during processing. Pharmaceutical quality systems are still often built up on heavy end-product testing philosophy, which is not promoting the use of process analytical technologies (PAT). This end-product testing does not provide insight into the dynamic processes occurring during processing. However, it is highly recommended to consider including PAT thinking into design of AM-based production and quality control.

Experimental work or intensive exploratory data science approaches will lead to a “dummy” mathematical model or identification of correlations in a system. It should be noted that this approach does not automatically lead to understanding the system behavior. However, the DoE results or exploratory data sciences can be utilized in increasing the mechanistic understanding of the system. This understanding is referring to understanding the fundamental physical and chemical phenomena occurring in the process. Wang et al. has demonstrated this with an example on binder jetting 3D-printing process (Wang et al. 2022). This process involves many physical and chemical phenomena occurring simultaneously, including dissolution, recrystallization, formation of liquid bridges, and consideration of gravitational effects.

In the literature related to more classical processing and the well-established unit operations within solid dosage forms, the use of processing regime maps has been suggested. In the wet granulation process, granule growth regimes such as steady growth, induction, nucleation, crumb, and slurry can be defined (Iveson and Litster 1998). This regime map can be further used to design and control wet granulation processes. Similar thinking would be important to include in the design and process control of innovative AM-based products (Fig. 5.6).

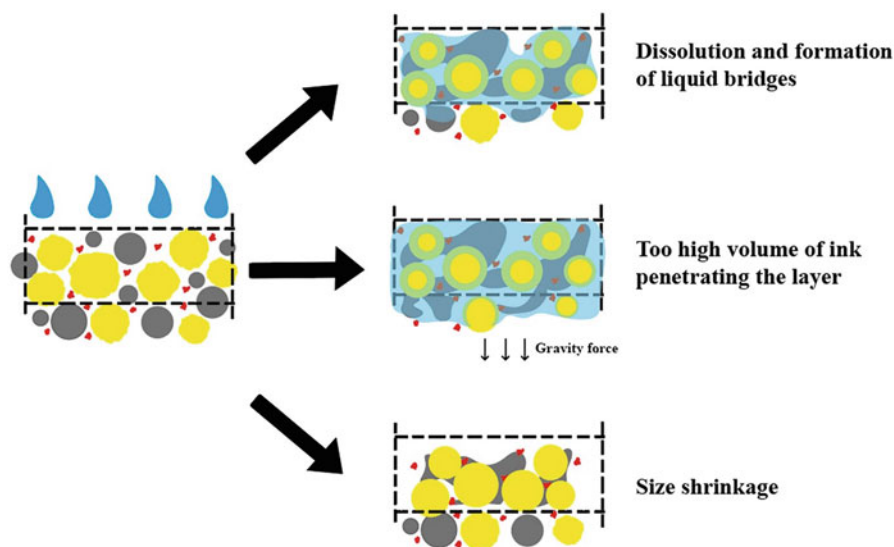


Fig. 5.6 Schematic illustration of the physical phenomena occurring during binder jetting 3D-printing process. The blue droplet is illustrating ink, the grey solid circle is polyvinylpyrrolidone particle, the yellow solid circle is lactose particle, the red dot is model API (paracetamol), and the black square in dash line is referring to the designed printed area. (Reprinted from Wang et al. 2022 with a permission from Elsevier)

Another important element allowing for improving the mechanistic understanding (or process understanding) is the use of PAT tools. The PAT concept is becoming a well-established regulatory concept, and some pharmacopoeia documents define the use of this concept. European Pharmacopoeia has introduced the general monograph 5.25 process analytical technology giving a framework for structured process analytics. Since the late 1990s, spectroscopic tools have been intensively implemented for this purpose, and near-infrared (NIR) spectroscopy is an example of broadly used PAT solution. The selection of spectroscopic solutions for PAT purposes has expanded and other spectroscopic tools, e.g., IR, Raman and terahertz (THz) can also be considered a routine solution for process analytics. These methods allow for fast nondestructive and noncontact quantification of the active substance in product, which is an ideal analytical solution for AM-based production systems (Trenfield et al. 2018). Spectroscopic tools can also be used for troubleshooting solid form diversity (amorphous/crystalline, salt, co-crystal, hydrate), as well as linked to physical properties (porosity and density differences) in the product. These methods can also be operated in a mapping mode providing a chemical map of the product.

Moving the analytical instrumentation toward production environment and reducing the off-line analytics of the end-product will inevitably increase the amount of data. This requires the implementation of multivariate data analysis tools. Principal component-based methods are well-established solutions for handling larger

amounts of data. However, it should be noted that more complex data scientific tools, including AI-based solutions, are increasingly used for analyzing the process analytical data.

5 Control Strategies

An ultimate step in the QbD-based product design is implementation of control strategy. The concept of control strategy is referring to a solution ensuring that the process performs as it should and maintains the predetermined quality. The previous steps of QbD (defining the TPP, exploratory phase, and gaining mechanistic understanding) are needed to make a control strategy. While contrasting the AM-based production with already existing production solutions, this can be a more challenging task. Moving away from the classical powder-based processing requires rethinking of the whole product design. AM-based processing can involve more than particle analysis and powder characterization; e.g., in case of FDM processing, the analysis of molten mixtures of polymer and the active substance is important. Figure 5.7 is providing an overview of quality characteristics related to an FDM printed dosage form, with examples of characterization tools needed for providing a full QbD picture from the product.

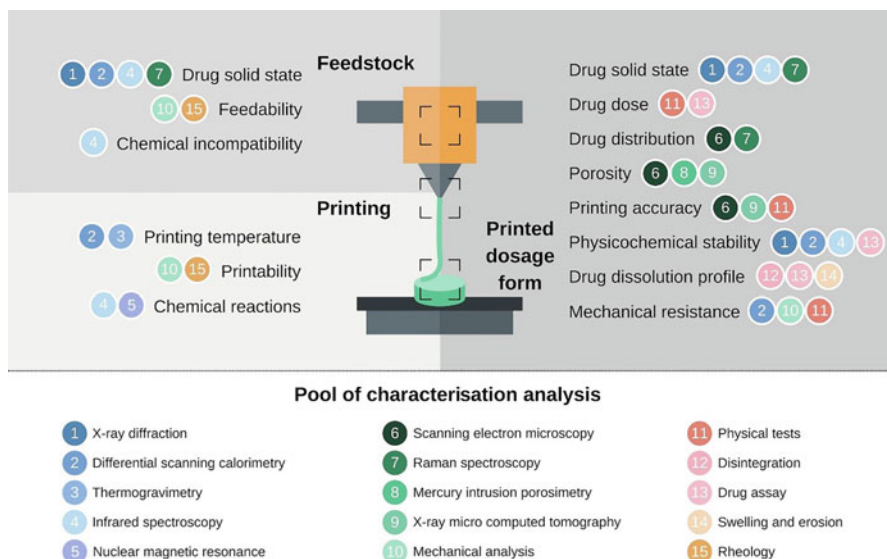


Fig. 5.7 The complexity of AM-based product design as exemplified with fused deposition modeling (FDM)-based product design. (Reprinted from (Deon et al. 2022) with a permission from Elsevier)

Implementation of real-time release testing (RTRT) principles is an attractive control strategy. However, it requires a combination of the off-line analytics and PAT solutions. It is crucial to explore the effect of potential sources of variation and build up process control solutions allowing for adoption to this variation. A properly selected PAT probe can provide fast detection of variation, and based on this observation, a process control loop can be implemented to adjust the process. Process control is a well-developed field of engineering, where there are several established solutions for building up a control loop for a given process. These methods are not fully implemented in the field of AM-based production of individualized products, and it is highly recommended to consider implementation of process control and RTRT thinking into new products. Future control strategies can also be based on AI and machine learning, because many of the interactions have a nonlinear nature.

6 Future Considerations

Pharmaceutical field is moving toward more individualized products and the number of product variants will inevitably increase. This requires the implementation of mass customization principles instead of the current mass production model. AM-based production of individualized products can be a game-changer in the pharmaceutical field, because it allows for more freedom in designing the final product structure and ultimately, improved individualized therapies for the benefit of the patients. In this context, the modular design will be an important design principle (Siiskonen et al. 2020). There is no reason to make an individualized product for each and every patient but rather to design building blocks with, e.g., “LEGO principles” (Rycerz et al. 2019). This will challenge the existing supply chain models (Lind et al. 2017): a potential solution for solving these challenges is the implementation of distributed production models. These distributed production solutions provide interesting challenges for implementation of QbD principles. Local production units might have limited resources to a full QbD implementation, which is underpinning the importance of carefully building the quality into this production setting. Modular design, where part of the products/modules are manufactured in a centralized and larger production facility might provide a solution for this challenge. The fast development of analytical instrumentation, especially handheld spectrometers, will provide a new view into quality control. At the same time, there is a growing interest to implement continuous manufacturing principle to pharmaceutical production. Continuous manufacturing of modules that are distributed to local production units where they are assembled according to the individualized needs of the local patient population is one potential business model.

Integration of the product to DTx and digital health environment is a fascinating scenario. The fundamental design principle of the existing medicinal products is a key obstacle for implementation of individualized therapies and digital health solutions. New innovative ideas and product design principles for solid oral products

allow for manufacturing-on-demand of connectable mass customized products. The healthcare sector is becoming more digitalized at all levels. In this development, the weakest link at the moment is the medicinal product itself – a plain white tablet without secure recognition elements cannot be connected to the future digital health environment. Designing modular products with connectable and secure recognition elements will be a technical solution for this. It is important to include the digital dimension of the product into the QbD-based approach already in beginning and clearly define this in the product TPP.

Process modeling and simulation have reached a totally new level with the recent development of computer performance and computational methods. It is very logical to include simulation into AM-based processing, because it naturally includes computer (in silico)-based design of the product structures. The properties of these products (mechanical, processability, drug release, stability) can be simulated at different levels (Boetker et al. 2016). Starting from the molecular scale, molecular dynamics can be used to understand polymer-active substance interactions. Discrete element modeling and finite element method are examples of methods allowing for simulations at a bulk scale. Simulation tools are becoming more accessible with the introduction of software packages containing graphical user interfaces and requiring less programming experience.

7 Learning of the QbD Principles with Independent Student Projects

A model for constructing a course is suggested. It should be noted that this suggestion can be naturally modified to fit into the existing curriculum. In this model, students are divided in smaller groups, and they work independently in these groups. It is expected that the participants of this course are at the later phase of their M.Sc. level education. This course can also be adjusted to a Ph.D. course level or continuous education type of module.

Work is performed in structured subprojects, where the work follows the workflow of a typical QbD approach (Fig. 5.8). It is expected that students identify a right AM processing solution for a given drug delivery challenge and critically evaluate and discuss this solution from an individualized product perspective. Suggested teaching methods include, but do not limit to:

1. Flipped classroom type of introduction of subprojects
2. Practical (hands-on) laboratory work with a goal of printing a prototype of the suggested product and analyzing critical quality attributes of the product
3. Classical lectures introducing the AM principles, individualization aspects (e.g., pharmacogenetics), digital health, and similar topics depending on the local curriculum
4. Final conference day where students present their projects

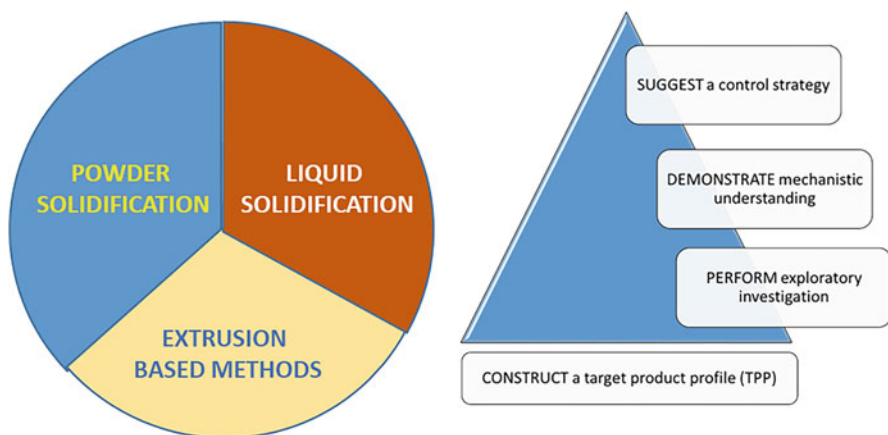


Fig. 5.8 Overview of the existing AM methods (left) together with different subprojects for learning of the QbD principles

The expected learning outcome of this project is that students can independently design a production solution for individualized product based on AM processing.

First Subproject: TPP

Students are given a written assignment including drug delivery challenge for a patient population. They are expected to construct a target product profile (TPP) for this product and suggest AM-based production solution for the potentially individualized product. Students should clearly justify their selection of a production method and the need for individualization.

Second Subproject: Exploratory Phase

Students should perform risk assessment of the selected AM production solution. In this phase, a qualitative method, such as Ishikawa diagram, based on the existing literature is recommended. After collecting this risk overview, students should get hands-on experience in the laboratory and print the first prototypes. This can be supported by implementation of design of experiments plan, when students have gained practical experience with the AM method.

Third Subproject: Mechanistic Understanding

Experimental work should be taken to the next level: it is crucial that students capture the physical and chemical phenomena occurring during the given AM process and demonstrate mechanistic understanding of these phenomena. This typically requires additional literature search and can be supported by additional experimental and analytical laboratory work.

Fourth Subproject: Control Strategy

In this subproject, students should summarize the suggested AM production solution at a commercial including number of patients, production speed, and supply chain model. This should also include discussion about the quality control solution for the final product.

The best outcome for the learning can be expected, if students get a possibility to present their project for a larger audience. In this day of presentations, it recommended to structure the day to follow a normal scientific conference.

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Chapter 6

Material Properties and Selections for Additive Manufacturing (AM)



Marcos Akira d'Ávila, Bruna Maria Manzini, and José Luis Dávila

Abstract Additive manufacturing is a technology that has revolutionized how objects are fabricated. In the last years, the pharmaceutical industry directed its attention to AM technologies, aiming to manufacture medications and devices with advantages such as customization, on-demand manufacturing, reduction of waste, and development of new medications and treatments in shorter times. This chapter presents the materials used for each AM technology, where their form and properties should be in good accordance with the process working principle. This fact defines the materials selections used as the basis to develop pre-formulations for tablets or to fabricate drug delivery devices. Furthermore, an overview of the main applications and future perspectives of pharmaceutical manufacturing and personalized drug delivery are discussed.

Keywords Materials · Thermoplastic polymers · Hydrogels · Extrusion · Thermosets · Filaments · Pellets

1 Introduction

Additive manufacturing (AM), popularly known as three-dimensional (3D) printing, is a group of processes in which successive layers of material are joined to form a 3D object (International Organization for Standardization/American Society for Testing and Materials 2015). This technology has been widely applied from prototype fabrication to functional parts fabrication. Nowadays, AM is a well-established and representative tool for automotive, aerospace, medical devices, implants, tissue engineering, dental, biomedical, and consumer goods research and applications

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(Norman et al. 2017; Rahman et al. 2018; Xu et al. 2021; Awad et al. 2018). The main advantages of AM comprise the fabrication of complex shapes, the capability to fabricate custom parts, repeatability, and the possibility to use different types of materials, which depends on the working principle of each AM process.

There is a growing demand for technologies that enable pharmaceutical manufacturers to offer patients effective and customized treatments. As a result, several researchers are investigating the technological options applied to health, with results that converge to using AM as a promisor technology for drug delivery devices and drug fabrication. For example, in 2015, the US regulatory agency Food and Drug Administration (FDA) approved the first 3D-printed tablet, called SPRITAM[®], which highlighted the use of 3D printers in this market (Norman et al. 2017; Preis and Öblom 2017; US Food and Drug Administration 2013). Since then, the interest in using AM for pharmaceutical manufacturing has been continuously increasing, also creating the necessity to develop 3D printers with specific characteristics for this area.

The main advantages associated with the use of AM technologies in the pharmaceutical area include the following:

- *Customization*: Complex morphologies, medications with different sizes and formulations, and modular drugs (Awad et al. 2018; Okwuosa et al. 2018).
- *On-demand manufacturing*: In situ fabrication of drugs according to the patient's requirements and dosage (Andreadis et al. 2022; Awad et al. 2021).
- *Reduction of waste (small-batches production)*: Traditional fabricating methods usually require high-scale production, which could create drug waste (Pavan Kalyan and Kumar 2022).
- *Development of new drugs and therapies in lower times*: The small-batches production allows the use of 3D printers as powerful tools for efficiently fabricating drugs. This can contribute to bringing new therapies to the market in a short time (Boniatti et al. 2021).

With that context, it is essential to highlight that patients could significantly be benefited, primarily sensitive patients such as pediatric and geriatric, who usually do not have suitable formulations available in the market. The latter can affect the treatment efficiency or generate toxic effects due to dosing (Karavasili et al. 2021; Goyanes et al. 2015). Thus, one of the targets in this field is using 3D printers as point-of-care devices; the drugs could be fabricated where required and according to the patient's dosage needs.

The fabrication of drugs and devices by AM can be performed according to the working principle of each technique, which will define the material properties and selections. According to the standard ISO/ASTM 52900 (International Organization for Standardization/American Society for Testing and Materials 2015), which establishes the terminology for AM, there are seven categories of AM processes:

- (i) Material extrusion
- (ii) Material jetting
- (iii) Powder bed fusion

- (iv) Binder jetting
- (v) Vat photopolymerization
- (vi) Sheet lamination
- (vii) Directed energy deposition

This book chapter will address the material properties of processes (i) to (v), considering that those technologies have potential applications in the pharmaceutical field. In Sect. 2 are presented the fundamentals of the materials used for AM technologies, focusing on the pharmaceutical manufacturing area. Next, Sect. 3 describes the AM working principle and the materials used for each technology. Subsequently, Sect. 4 presents an overview of the applications. Finally, future perspectives and closing remarks are presented. As described here, the materials selections and properties are directly linked with the AM process; the working principle of each technique defines the form of the raw material and the required properties, which allow its structuration in layers. As logical, the AM technique should not affect the efficiency of the drug active principle of the final product.

2 Materials Properties and Selections

Polymers are widely used in the pharmaceutical industry; they are usually defined as macromolecules formed by repeating units covalently bonded along the whole polymer chain. In general, they can be classified into thermoplastics, elastomers and thermosets (Tan et al. 2020); a wide range of polymers is available with different properties and characteristics, making it possible to process them by different AM techniques (Stansbury and Idacavage 2016; Dizon et al. 2018; Gibson et al. 2021). Considering the processing principle for each AM technique, polymers can be processed starting from a thermal reaction bonding or a chemical reaction bonding. Then, the material used for each AM technique could be in different forms, such as filaments, pellets, powders, high viscosity or shear-thinning inks, and photosensitive resins, among others. Figure 6.1 presents an overview of different AM techniques used for polymer processing, specifically for drug 3D printing. These techniques are described in Sect. 3.

Below are the fundamental definitions related to the different materials used in additive manufacturing:

2.1 *Thermoplastic Polymers*

Thermoplastic polymers are moldable; they flow as a highly viscous fluid when heated and solidify when cooled. Their molecular structure is quite simple: they are formed by independent macromolecules (polymer chains), which are associated by intermolecular forces. These forces weaken when the temperature increases, turning

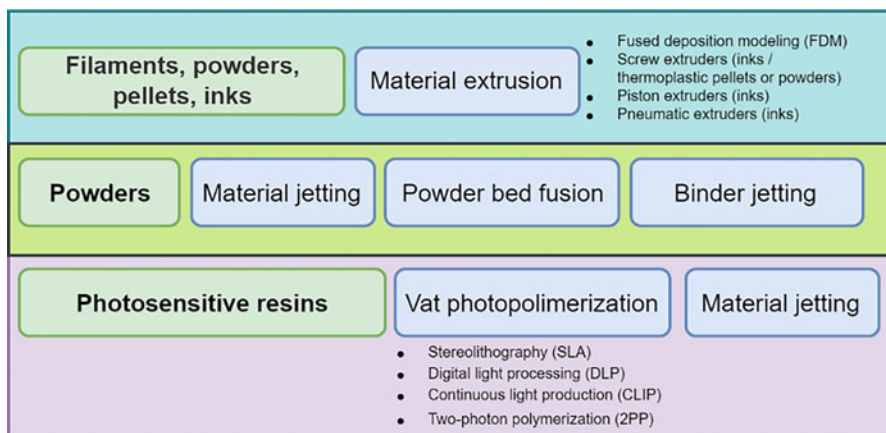


Fig. 6.1 Additive manufacturing (AM) techniques for polymer processing

the material moldable. Usually, melt temperatures are in the range of 100–250 °C. This characteristic makes thermoplastic polymers attractive for different industrial applications because they can be reprocessed and recycled multiple times (Biron 2018; Grigore 2017), however, with loss in their physical properties due to partial chain degradation. Thermoplastics can be subclassified into amorphous, crystalline, and semicrystalline polymers.

In amorphous polymers, the molecular chain formation is random, and polymer chains are randomly interlaced. In this case, chain mobility is determined by the glass transition temperature T_g , which is a second-order transition. Above this temperature the chains gain mobility resulting in a flowable material, which allows processing such as extrusion and molding (Rudin and Choi 2012).

Contrariwise, crystalline polymers present an organized molecular structure, and semicrystalline combines amorphous and crystalline regions. In general, semicrystalline and amorphous polymers are found in most applications, whereas 100% crystalline polymers are unlikely to be found in commercial thermoplastics. For molding semicrystalline polymers, they have to be heated above the crystalline melting temperature (T_m), which is the temperature where the transition from the crystalline structure to an amorphous conformation is obtained. Crystalline melt temperature is higher than glass transition temperature and is a first-order transition since it involves changes in the conformational state of the chain molecules (Rudin and Choi 2012).

Therefore, melting in thermoplastics involves distinct molecular mechanisms for amorphous and semicrystalline polymers, which are associated with T_g and T_m , respectively. This fact leads to different melting behavior regarding temperature ranges: amorphous polymers melt in a wide range of temperatures, while semicrystalline polymers present a melting point. This melting point is well-defined when the degree of crystallinity increases (Gibson et al. 2021).

Thermoplastic materials are widely used for AM material extrusion processes; fused deposition modeling (FDM) is a well-established process that uses thermoplastic filaments (Melocchi et al. 2015; Eleftheriadis et al. 2019; Verstraete et al. 2018). Similarly, thermoplastic pellets and powders are used as raw materials for screw extruders (de Castro Silveira et al. 2014; Justino Netto and Silveira 2018). FDM and screw extrusion are also known as hot melt extrusion processes. Furthermore, some research reports the use of solvents to dissolve thermoplastic polymers. Piston-based mechanical or pneumatic systems are used to deposit these solutions; they are deposited while the solvent evaporates rapidly, which allows the 3D-printed object structuration (Prasophum et al. 2019). Also, thermoplastics can be used for material jetting and powder bed fusion processes (Ligon et al. 2017).

For drug manufacturing, the active principle should be homogeneously dispersed in the polymer raw material. Moreover, it should maintain its properties after the thermal reaction bonding or solubilization. Thermoplastics act as drug carriers; different polymers can be used for this purpose, for example, polyethylene oxide (PEO), polyethylene glycol (PEG), poly(vinyl pyrrolidone) (PVP), poly(vinyl alcohol) (PVA), polycaprolactone (PCL), and polyurethanes (PU) (Tambe et al. 2021). Also, cellulose-based polymers have been used in extrusion-based processing, such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC AS), hydroxypropyl methylcellulose phthalate (HPMC P), and ethylcellulose (EC). Furthermore, the use of commercial copolymers has been reported as drug carriers for melt extrusion printing, such as vinylpyrrolidone/vinyl acetate copolymer (Kollidon[®] VA), dimethylaminoethyl methacrylate copolymer (Eudragit[®] E), and vinylcaprolactam/vinyl acetate copolymer (Soluplus[®]).

As found in most industrial applications of thermoplastics, plasticizers are widely used in pharmaceutical applications to tune properties such as processing temperature, viscosity, hydrophilicity, and mechanical properties (Tambe et al. 2021). Plasticizer acts as lubricants and can be waxy or low-molecular-weight compounds. Plasticizers used in drug dosage formulations are phthalate, fatty acid esters, citrate esters and sebacate esters, vitamin E TPGS, propylene glycol, triacetin, polysorbates, docusate sodium, and other surfactants (Stanković et al. 2015; Almeida et al. 2012).

Reports in the literature have shown the use of thermoplastic formulations for dosage forms of different drugs using 3D-printing technologies. For example, different thermoplastic formulations were reported in developing dosage forms of carvedilol (Ilyés et al. 2019), pramipexole, baclofen, and hydrochlorothiazide (Gültekin et al. 2019; Palekar et al. 2019; Nukala et al. 2019).

2.2 Thermosets

Thermosets are polymers with high-density cross-linking, where a three-dimensional network is formed between the polymer chains due to chemical bonding. In general, thermosets are obtained by mixing prepolymers, which are usually monomers or

oligomers in liquid form, together with a catalyst or initiator, which promotes polymerization and cross-linking when the reaction is initiated by submitting the system to appropriate conditions, e.g., temperature, UV radiation, etc. The chemical bonding resulting from high-density cross-linking is known as curing and is an irreversible process. As a result, thermosets do not melt when heated. These materials are rigid and commonly used in applications that require high mechanical strength (Sastri 2022), although the brittleness of thermosets may limit the range of applicability. In order to improve ductility and flexibility, resins based on polymers with high chain flexibility can be used. Cross-linking with methacrylated flexible chain polymers has been reported, resulting in elastomer-like materials with high elasticity and flexibility, such as methacrylated PCL (Zarek et al. 2016) and siloxane (Patel et al. 2017).

For AM processes, there are available photopolymerizable prepolymer resins, which are known as photocurable resins. These liquid resins are commonly formed by high-molecular-weight monomers and oligomers, a photoinitiator, and other additives (Gibson et al. 2021). A UV light system usually initiates the cross-linking process. Current pharmaceutical research widely uses thermosets and AM processes to manufacture drug release and other medical devices.

Photocurable resins used in pharmaceutical applications are mainly based on methacrylated and acrylic esters multifunctional monomers (Xu et al. 2021). These resins are used in vat photopolymerization (see Sect. 3.5), which allows the manufacturing of parts with higher dimensional accuracy. Examples of applications of thermoset resins are found in the manufacturing of microneedles (Economidou et al. 2019), dental applications (Yue et al. 2015; Piedra-Cascón et al. 2021), and drug delivery systems with complex geometries (Vaut et al. 2020). Some challenges in using thermosets in pharmaceutical applications can be found in problems associated with monomer residues after cross-linking (Oskui et al. 2016) and drug reaction during resin photopolymerization (Hori et al. 2019).

2.3 Hydrogels

Hydrogels are cross-linked-hydrophilic polymers that can absorb and retain high amounts of water, sometimes up to thousands of times their dry weight (Hoffman 2012). The cross-linked three-dimensional network of these materials presents a viscoelastic behavior that provides a degree of flexibility, which in some cases is similar to the natural tissues (Gulrez et al. 2011).

Taking into account the cross-linking mechanism, hydrogels can be physical or chemical. Physical gels easily degrade, disintegrate, and dissolve; molecular entanglements or secondary forces form them, which include ionic cross-linking, hydrogen bonding, or hydrophobic interactions. These gels can form hydrogels when the secondary forces restrict the polymer chain's movement. Physical hydrogels are reversible because the cross-linking points can be easily broken due to weak interactions. Contrariwise, chemical hydrogels are formed by covalent cross-linking,

which is stronger and more stable. Hydrogels can be obtained from synthetic or natural sources, and both types find pharmaceutical applications.

These materials are widely used with material extrusion AM processes due to the shear-thinning behavior and the viscoelastic properties of the prepolymer formulations, which allow extrusion at lower temperatures (Reddy and Sharma 2020). Moreover, they can also be used with vat photopolymerization processes in equipment particularly developed for these materials. In this case, photoinitiators generate chemical cross-linking during the process (Xu et al. 2021). Different types of hydrogels obtained from either extrusion or vat polymerization were studied for drug release systems. For example, polysaccharides (Li et al. 2018; Zamboulis et al. 2022) and PEG (Jacob et al. 2022) drug delivery systems can be obtained from extrusion printing. On the other hand, in vat polymerization, methacrylate cross-linked hydrogels can be used (Xu et al. 2021).

It is also important to highlight that research oriented toward developing novel drug release systems is taking advantage of hydrogel bioprinting technologies. In this case, drug screening studies can be performed using organ-on-a-chip and cell-laden models for in vitro drug testing (Lim et al. 2018).

3 Additive Manufacturing Techniques

3.1 *Material Extrusion*

As illustrated in Fig. 6.2, in the material extrusion processes, the material flows through a nozzle and is selectively dispensed on a construction platform. For this technology, materials such as thermoplastic filaments, powders, and pellets can be used; the material is heated and molten in an extruder and then dispensed (Fig. 6.2a, b). Furthermore, semisolid materials, which include gels, hydrogels, and pastes, can also be used with this technology. The extrusion system is usually based on a pneumatical or mechanical-driven piston (for semisolid materials) (Fig. 6.2c, d), a screw system (for thermoplastic powders, pellets, or highly viscous semisolid materials) or a gear-roller system (for thermoplastic filaments). For pharmaceutical applications, the active principle should be dispersed, where the main limitation for thermoplastic-based formulations is the processing temperature, which can cause thermal degradation and affect drug stability (Gibson et al. 2021; Hsiao et al. 2018).

3.2 *Material Jetting*

The material jetting process, illustrated in Fig. 6.3, is based on the 2D inkjet working principle. For that reason, this technology is also known as inkjet 3D printing. In this case, a jet of droplets is selectively deposited layer by layer. This technology can use different materials, including photocurable resins (Fig. 6.3a), molten polymers

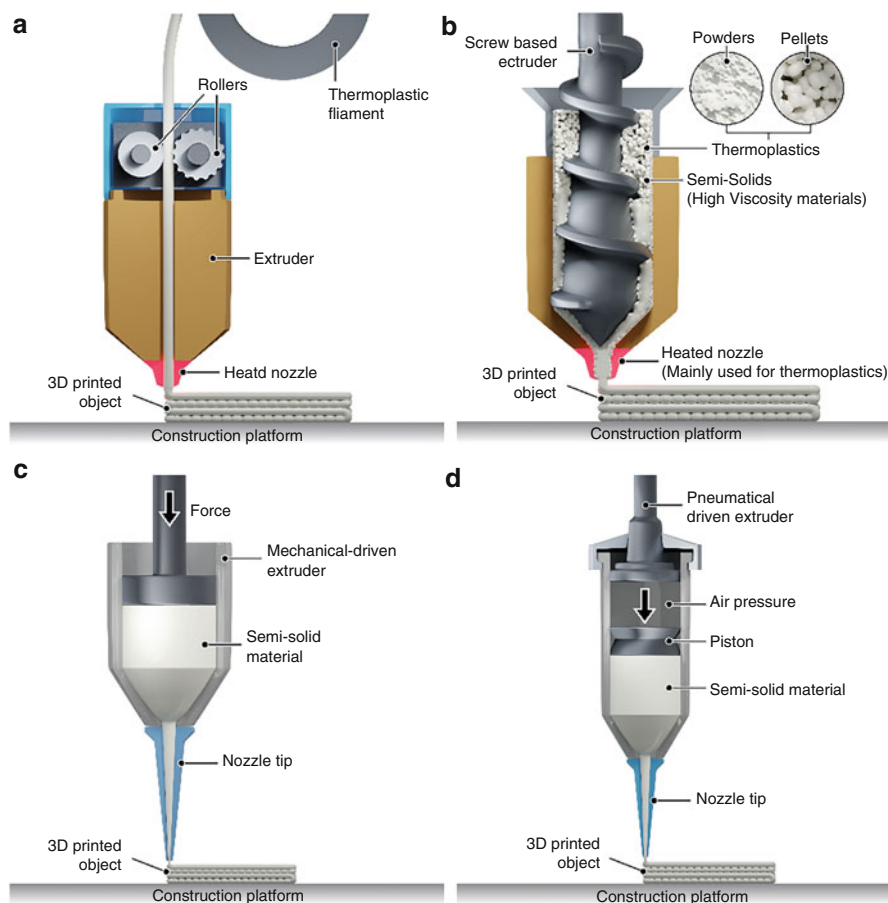


Fig. 6.2 Material extrusion variations for different types of materials: (a) fused deposition modeling (FDM) extruder, (b) screw extruder, (c) mechanical-driven extruder, and (d) pneumatically-driven extruder

(Fig. 6.3b), waxes, solutions, suspensions, ceramic suspensions, and molten metals (Basit and Gaisford 2018; Awad et al. 2020). For drug 3D printing, some challenges are associated, where the formulation should be planned to be dispensed by jetting and subsequently solidified by some physical or chemical mechanism.

3.3 Powder Bed Fusion (PBF)

This technology allows the production of objects starting from powder materials; a thermal energy source is used to melt the surface particles, which fuse between them in each layer. Then, the object is formed layer by layer. Selective laser sintering

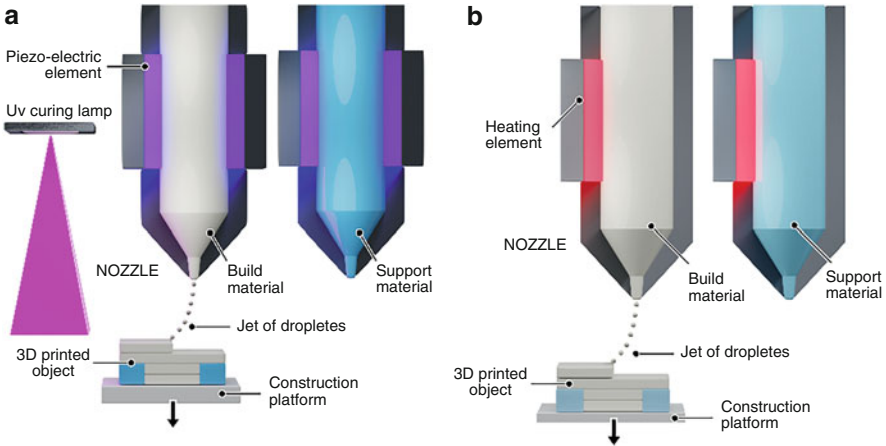


Fig. 6.3 Material jetting process: (a) piezoelectric-based deposition system and (b) heating-based deposition system

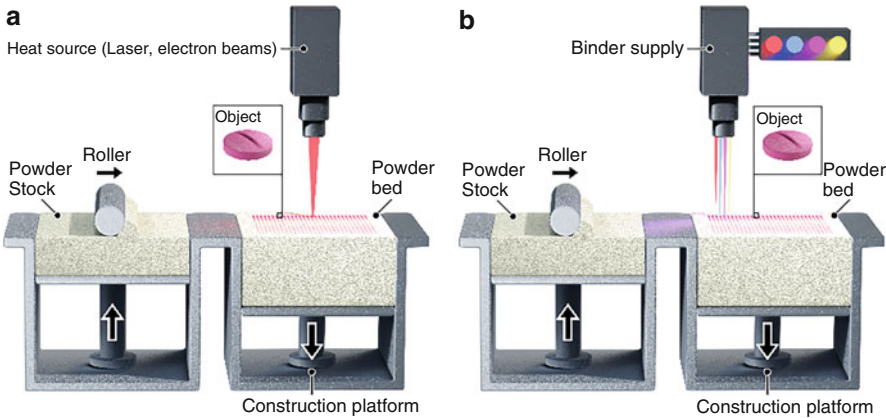


Fig. 6.4 (a) Powder bed fusion (PBF) and (b) binder jetting processes

(SLS), illustrated in Fig. 6.4a, is a PBF process that uses a laser beam. For pharmaceutical applications, SLS is applied using a powder blend composed of a thermoplastic polymer and a drug dispersed (Sharma et al. 2022).

3.4 Binder Jetting

As illustrated in Fig. 6.4b, binder jetting is similar to PBF. Nevertheless, in this case, a liquid bonding agent is used to bond the powder materials; for this process, the

mechanical strength of the fabricated objects is lower when compared with other processes, such as SLS or FDM.

3.5 Vat Photopolymerization

In the vat photopolymerization technique, a liquid resin is selectively cross-linked by light irradiation (Quan et al. 2020). This working principle encompasses different technologies, such as stereolithography (SLA) (Fig. 6.5a), digital light processing (DLP) (Fig. 6.5b), continuous liquid interface production (CLIP) (Fig. 6.5c), and

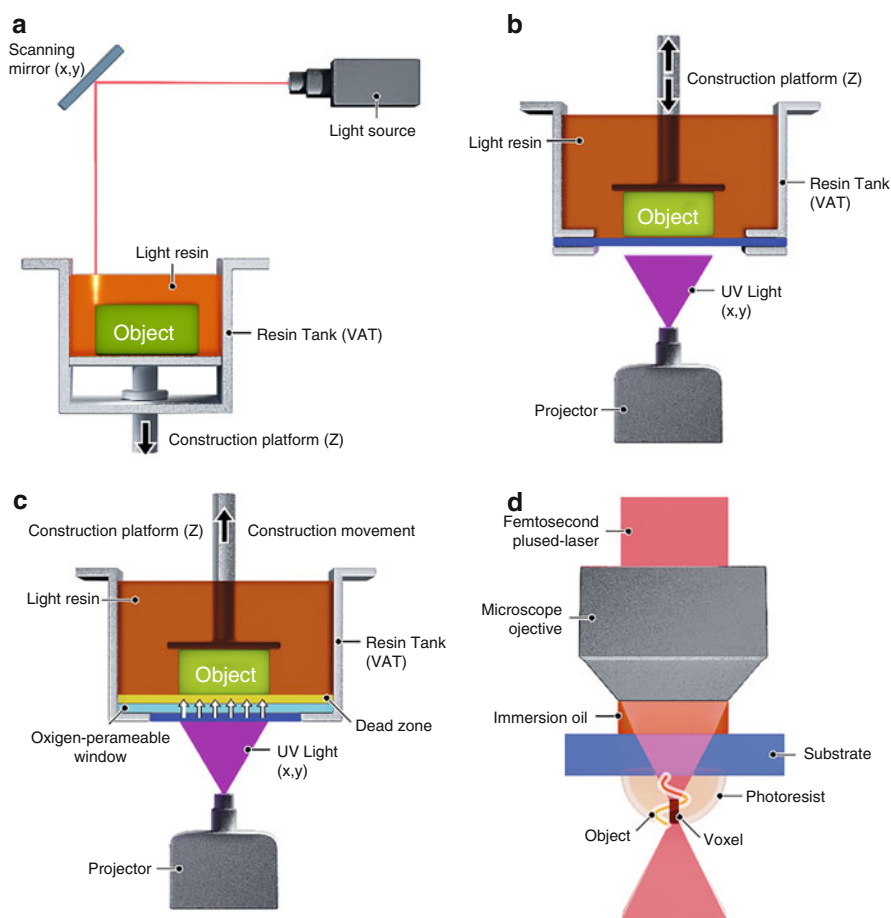


Fig. 6.5 Vat photopolymerization processes: (a) stereolithography (SLA), (b) digital light processing (DLP), (c) continuous liquid interface production (CLIP), and (d) two-photon polymerization (2PP)

two-photon polymerization (2PP) (Fig. 6.5d). The SLA technology uses a laser beam as the light source. The DLP technology uses a digital light projector, making the process faster. Similarly, the CLIP technology also uses a digital light projector; nevertheless, an oxygen permeation membrane is used to help the continuous 3D printing; thus, the process is even faster (Otuka et al. 2021). Furthermore, in 2PP, a pulsed femtosecond laser is used. In this case, a near-simultaneous absorption of two photons initiates a chemical reaction between a photoinitiator and a monomer; then, polymerization occurs. Here is essential to highlight that two-photon absorption is a nonlinear optics phenomenon, where the light intensity attenuation is confined to the laser focal volume. Then, polymerization only takes place inside the focal volume, allowing the fabrication of high-resolution submicron objects (Lunzer et al. 2022; Xing et al. 2015; Revilla-León et al. 2019). The materials used for vat polymerization are photosensitive resins, which are basically composed of monomers or oligomers (based on methacrylates or acrylic esters) and a photoinitiator (Wang et al. 2016); for pharmaceutical applications, a drug active principle is added to the formulation. Furthermore, photosensitive hydrogels can also be used with these processes.

4 Applications and Future Perspectives

The growing interest in AM research for applications in different fields encouraged this technique's application in the pharmaceutical area, which aligns well with personalized medicine's advances. Currently, most efforts are concentrated in the research and development phase: regulatory aspects faced by pharmaceutical products and the long process until its approval by the health regulatory agencies delays going to the market. Therefore, the use of AM in the pharmaceutical sector is mainly directed toward two types of research: AM for drug delivery and AM for producing drug testing systems.

The use of AM to develop pharmaceutical forms can modify bioavailability; for example, the production of tablets by material extrusion 3D printing allows varying filling densities and other morphological characteristics, which modify the drug release profile (Norman et al. 2017; Lim et al. 2018). In addition, complex geometries can make multifunctional pharmaceutical products with different drug release kinetics, allowing the release at different pH levels. The hydrophilic polymers with a pharmaceutical grade are essential factors, for example, in the composition of controlled release dosage forms.

Another advantage involved is the possibility of printing dosage forms that consider the patient's anatomical characteristics, mainly aimed at specific subjects such as individuals who have difficulty swallowing, including the pediatric and geriatric populations. It is expected that the difficulty in swallowing causes poor adherence to treatment, especially when the drug has low palatability and requires frequent doses. These challenges have guided research into the use of AM for the development of tablets and other easy-to-swallow oral dosage forms (Wu et al. 2009).

3D printing for pharmaceuticals is not limited to producing oral administration forms. Several other forms can be produced by AM, such as transdermal and rectal and vaginal drug delivery systems. Researches range from the production of nasal patch for acne treatment to microneedle patches for insulin release. 2PP 3D printers have higher resolution, which allows the fabrication of fine microneedles capable of penetrating the skin and delivering drugs to the cells. Rectal and vaginal device production points to suppositories, intrauterine devices, and surgical meshes. Also, stents, vaginal dilators, and pessaries can be developed. These medical devices consider essential patient characteristics which directly influence the effectiveness and adherence to treatment: anatomy, gender specificity, age, clinical conditions, menstrual cycle, menopause, and pregnancy. Thus, it is possible to customize the medication according to the patient's morphology and the correct dose.

Moreover, desktop or transportable 3D printers enable carrying out the AM process where medicines are required. Consequently, the products can be printed in healthcare facilities, such as hospitals, emergency rooms, pharmacies, and clinics, which represents an advantage in terms of easiness in execution and accessibility for small spaces.

Of course, the drug choice is guided by the purpose of the treatment for which it is intended. Nevertheless, it limits the choice of drugs suitable for 3D printing, especially when substances are sensitive to light and heat. However, approaches try to minimize this problem, such as the microencapsulation of drugs in polymers and the incorporation of drugs after the printing process is complete. In SLS printing, it is possible to overcome the sensitivity problem by mixing the drug with a polymer with high laser absorption.

Compared with other AM technologies, SLS did not arouse much interest from researchers; the possibility of drugs and excipient degradation and the scarcity of approved materials for pharmaceutical use involve some challenges. However, this safety issue involving the material contributed to research for developing drug powder mixtures, for example, thermoplastic polymers that enable therapeutic product manufacturing by SLS. Also, they permit the production of drugs without solvents, eliminating additional drying steps.

Challenges associated with using AM in the pharmaceutical area must be overcome. Currently, medical devices and products fabricated by alternative technologies require a long time to be approved by regulatory agencies, a process that can take years or even decades to complete. Numerous regulatory requirements and the need for a specific guideline for AM in this sector make the approval process even more complicated, resulting in the absence of standard protocols to be followed during the device/dosage form manufacturing process. However, the Food and Drug Administration (FDA) regulatory agency has already approved medical devices and dosage forms after conducting clinical studies proving their effectiveness.

Additionally, the costs involved in the AM process can be highlighted as a disadvantage compared to the traditional drug manufacturing process. The high value of raw materials and the lack of a standard in the pricing of projects and manufacturing contribute to the low economic competitiveness of AM compared to other usual techniques in the pharmaceutical industry. Consequently, there is an influence on other aspects, such as the scalability of the process.

The industrial-scale production stands out as a challenge if we compare AM to the traditional methods used by the pharmaceutical industry to produce millions of pills per hour. To circumvent this “problem,” there are 3D printers that adjust the size of the structure and deposit the material in rolling conveyor belts, adapting to increase production. In addition, 3D printers on the market can achieve higher printing speeds, optimizing the manufacturing process. However, AM, for the production of drugs, focuses its efforts on personalization and small-batch production for conscious consumption. Thus, scalability does not represent a real problem for using AM for these purposes, nor does it represent the possibility of replacing traditional methods of industrial drug production in the medium-long term (Awad et al. 2020; Alhnan et al. 2016; Duan et al. 2011; Zhou et al. 2008; Duan and Wang 2010).

The second large group explores AM to carry out *in vitro* drug tests, which enables the replacement of animal trials and 2D models. The criticism involving preclinical experimentation, *in vivo* models with other species, the fight against animal abuse, and animal ethics issues aroused concern about developing new possibilities for drug testing. In addition, although some mammals have physiology very similar to humans, animal models do not represent what occurs in drug distribution and metabolism and can also present low reproducibility. Differently, 2D models, despite being a widely explored alternative, do not reproduce the morphological and genetic conditions of cells compared to 3D models. In a three-dimensional microenvironment, cells are found in a mimetic location that favors intercellular communication and contributes genetically to the production of membrane molecules and secretion of signaling factors. Additionally, 3D models present diffusion of gases and nutrients more biomimetic to accurate models when compared to 2D models.

AM techniques came to help overcome these challenges with 3D printing of gels, hydrogels, inks, bioinks, and pastes. Consequently, AM became one of the most applied approaches for producing biomimetic models of human body tissues. Medicine can benefit from models in different areas such as oncology, cardiovascular, ophthalmic, gastric, respiratory, infectious, and neurological diseases. For example, it is possible to print a device that simulates conditions to analyze how drug diffusion occurs, or drug release kinetics or drug deposition, by simulating drug application conditions in a specific area of the human body. Additionally, 3D models favor understanding the effectiveness of drugs, especially those related to the treatment of the pediatric population, which has different anatomy and physiology compared to adults.

Finally, drug testing can be performed with organ-on-a-chip models, printed mainly by soft lithography. These microfluidic devices can represent a single or multiple organs, representing a set of systems, such as gastric, vascular, epithelial, and even aggregating tumor development. These preclinical trials can benefit the understanding of new drugs' mechanism of action, the performance of toxicity tests, and the analysis of the metabolic conditions involved. Thus, organ-on-a-chip models increase the possibilities for the pharmaceutical sector, optimizing time and costs

and favoring the beginning of clinical trial (Awad et al. 2018; Lind et al. 2017; Hatton et al. 2015; Trenfield et al. 2018), reinforcing how AM can be a promising technology for the pharmaceutical area.

Questions

- (i) Thermoplastic filaments can be used with the following:
 - (a) Screw extruders
 - (b) **Fused deposition modeling (FDM) extruders**
 - (c) Binder jetting processes
 - (d) Digital light processing (DLP)
- (ii) Which of the following sentences does not fit within the advantages of additive manufacturing in the pharmaceutical field:
 - (a) Customization of drugs and devices
 - (b) Possibility of manufacturing modular drugs
 - (c) **High-volume manufacture of drugs and devices**
 - (d) Reduction of waste
- (iii) Vat photopolymerization processes use:
 - (a) Molten polymers
 - (b) A liquid bonding agent
 - (c) Powder thermoplastic polymers
 - (d) **Photocurable resins**
- (iv) Thermoplastic polymers are:
 - (a) **Widely used for AM material extrusion processes**
 - (b) Highly cross-linked
 - (c) Small molecules
 - (d) Not moldable
- (v) What of the following vat photopolymerization processes enables the fabrication of high-resolution submicron objects:
 - (a) Continuous liquid interface production (CLIP)
 - (b) Stereolithography (SLA)
 - (c) Digital light processing (DLP)
 - (d) **Two-photon polymerization (2PP)**
- (vi) Which of the following sentences is not applicable for hydrogels?
 - (a) Materials used in vat polymerization
 - (b) Materials used in extrusion-based 3D printing
 - (c) **Materials that do not present cross-linking**
 - (d) Materials with high hydrophilicity

- (vii) Which of the following sentences applies for thermosets?
- (a) Materials that are widely used in FDM
 - (b) **Materials with high cross-linking density**
 - (c) Materials with high melt temperature
 - (d) Materials with low melt temperature
- (viii) Polymers that do not present cross-linking are:
- (a) **Thermoplastics**
 - (b) Thermosets
 - (c) Elastomers
 - (d) Hydrogels
- (ix) The cross-linking mechanism of physical hydrogels is:
- (a) **Reversible**
 - (b) Covalent
 - (c) Irreversible
 - (d) Strong
- (x) Additive manufacturing in the pharmaceutical field:
- (a) focuses on drug-screening assays
 - (b) **enables several applications, which include oral administration forms, pharmaceutical devices, drug screening, modified drug release, etc.**
 - (c) enables several applications, which include oral administration forms, pharmaceutical devices, drug screening, modified drug release, etc.
 - (d) the high-scale production of personalized drugs

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Chapter 7

Preformulation of 3D Printable Pharmaceutical Dosage Forms



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Abstract Preformulation studies are designed to ensure a pharmaceutical dosage form will be produced within the best scenario of materials and processing conditions to guarantee the required performance and stability. In the context of medicines production by 3D printing, a preformulation protocol for 3D printable dosage forms needs to consider the particularities of additive manufacturing. This chapter proposes to draw guidelines for developing a protocol to perform preformulation studies of such 3D printable medicines. For this, an overview involving both physical and chemical characterization of materials combining several techniques, their fundamentals, and applications is provided. Criteria for designing a preformulation protocol adapted to the printing technology, the processing stages, and the drug product to be manufactured are discussed in light of possible characterization techniques. This step in developing 3D medicines should provide information on the chemical stability and physical properties of materials as well as on drug-excipient interactions. The 3D printing by fused deposition modeling will be the central point of this chapter since this technique is the most widely explored in the pharmaceutical field.

Keywords Preformulation · 3D printing pharmaceuticals · Infrared spectroscopy · Thermal analysis · Rheological analysis

1 Introduction

Additive manufacturing, also known as three-dimensional printing, has been employed in numerous production sectors in the last decades, but it has only recently been explored in the pharmaceutical field. Indeed, the first FDA-approved 3D printed medicine was only launched in August 2015 (West and Bradbury 2018). As in every beginning, it holds many opportunities and challenges.

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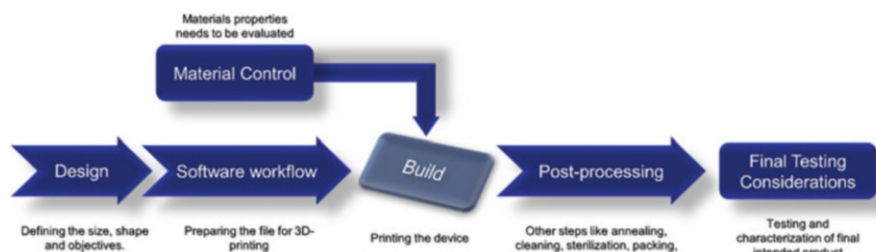


Fig. 7.1 Flowchart for additive manufacturing process according to FDA. (Adapted from US Food and Drug Administration (FDA 2017))

The main advantage of 3D printing for pharmaceuticals, highlighted in the latest research, is the possibility of obtaining personalized medicines by modifications in printable parameters such as size, shape, and internal structure (Awad et al. 2019; Cunha-Filho et al. 2017).

The pharmaceutical production of solid dosage forms using additive manufacturing technologies significantly differs from traditional production processes involving powdered materials. Generally, the development of a 3D printed dosage form involves a reasonable number of steps that vary depending on the 3D technology used and the application. These steps were outlined by Zhang et al. (2018) and adapted by Bhuskute et al. (2021) as follows:

- (i) Conceptualization and design
- (ii) Deconstruction/slicing (preparation of print files)
- (iii) Preformulation studies
- (iv) Instrument setup
- (v) Printing
- (vi) Cleaning and post-processing
- (vii) Application

The FDA established a similar process flow (Fig. 7.1) in the document entitled *Technical Considerations for Additive Manufactured Medical Devices* (FDA 2017), which classifies the necessary material characterization into:

- (i) *Material chemistry* – emphasizing that the manufacturing processes may result in unexpected or undesired material chemistries
- (ii) *Material physical properties* – once the interlayer secondary interactions are unique in additive manufacturing, determining the ultimate structural integrity of the finished device

Regarding the preformulation stage, there is abundant literature available on this subject. However, studies explicitly involving preformulation studies of 3D printable dosage forms are still quite scarce due to their recent character.

Some studies aiming to guide the production of medicines by fused deposition modeling (FDM) 3D printing have been recently reported (Pinho et al. 2021; Silva et al. 2022). In general, these studies have used techniques such as differential

scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-ray diffractometry (XRD), Fourier-transform infrared spectroscopy (FTIR), optical microscopy, and oscillatory rheometry to characterize the physical and chemical properties of the components and mixtures in different steps of the processing.

Nevertheless, the essential purpose of a pharmaceutical preformulation protocol is regardless of the production technologies involved. A reasonable preformulation investigation starts with an accurate selection of active pharmaceutical ingredients (API) and excipients, considering the match between the physicochemical properties, the processing, and the final application. The main objective of this crucial step of drug product development is to avoid incompatibilities and undesirable chemical or physical changes along the processing that can affect the integrity and performance of the final dosage form.

2 State-of-the-Art of Preformulation Studies in 3D Printing

Characterization of the physical and chemical properties of the raw materials and their mixtures, before and after the processing steps, is generally the most used approach in preformulation studies (Zhang et al. 2018; Pinho et al. 2021; Silva et al. 2022). For 3D printing technologies, the physical analyses of the materials, including thermal, mechanical, and rheological behavior, are gaining in importance (Lima et al. 2022; Shaqour et al. 2021; Quodbach et al. 2021).

Numerous studies establishing predictive models for 3D printing based on thermal and rheological properties have been reported (Shaqour et al. 2021). This strong correlation justifies the need to include the characterization of mechanical and rheological properties in a 3D printing preformulation study.

Furthermore, Lima et al. (2022) explore the mechanical analysis of polymeric filaments to evaluate the elastic limit and the extent of plastic deformation to fracture. In the evaluation of viscoelastic behavior, oscillatory shear rheology was used to study the melt deformation, especially at the temperatures chosen for printing. These data were used to determine the printability of filaments in tablet production by an FDM 3D printer. Conjointly, pharmacopeial limits were used to assess the quality of the 3D object.

On the other hand, accurate spectroscopic investigations have been carried out to investigate possible chemical changes in the FDM 3D printing process conditions. For example, Raman spectroscopy and solid-state nuclear magnetic resonance (SSNMR) have been recently used to evaluate the stability of the ramipril, concluding that the drug did not undergo degradation below its melting temperature; however, higher temperatures can convert the drug into the impurity diketopiperazine (Kollamaram et al. 2018).

Based on a novel thermal droplet deposition 3D printing technique known as *arburg* plastic free-forming, Eudragit[®] EPO with paracetamol has also been studied as a model system. FTIR data were used to support XRD patterns of the granules and

3D printed tablets, concluding that the granules' production process conditions affect the crystallinity of paracetamol at the surface and in the bulk of the granules (McDonagh et al. 2022).

A wide range of physicochemical characterizations have also supported studies involving machine learning, and artificial neural networks (ANNs) reported over the last few years. Such an approach has been demonstrated to be a powerful tool to accelerate the research and development of 3D printed pharmaceutical formulations, avoiding the laborious trial-and-error method (Elbadawi et al. 2021).

Currently, FDM 3D printing is one of the most widely studied technologies, among other 3D printing techniques in pharmaceutical sciences (Park et al. 2018; Barberis et al. 2022; Kim et al. 2022; Kollamaram et al. 2018). However, FDM 3D printing still presents many challenges, mainly due to successive heat processes that can strongly affect the physicochemical properties of the materials. Moreover, undesirable degradation products could be produced, compromising the safety and performance of the intended 3D printed dosage forms.

An appropriate physicochemical characterization at each step of the process can help to screen and understand any undesirable physical or chemical change due to processing conditions or incompatibilities between the components. For this purpose, a recommendable approach in FDM 3D printing is to characterize (i) physical mixtures before the extrusion process, (ii) filaments produced by HME, and (iii) printed form.

Based on this scenario, this chapter will focus on drawing guidelines to carry out preformulation studies of 3D printable pharmaceutical dosage forms, mainly but not limited to those produced by the FDM 3D printing technique. In addition, this chapter will provide a brief needful theoretical background about the associated characterization techniques.

3 The Chemical Nature of API and Excipients

Filaments for FDM 3D printing are commonly prepared by extrusion of the API and excipients. Hot-melt extrusion is a thermomechanical process in which the materials are subjected to simultaneous thermal and shearing stresses (Censi et al. 2018).

The internal friction during the extrusion can cause unexpectedly high local temperature increases, commonly known as shear heating (Forsters et al. 2021). For this reason, simulating actual extrusion conditions can be the key to obtaining extrapolated results in preformulation studies.

Therefore, several characterization techniques can be employed to investigate some possible undesirable chemical changes during the hot-melt process, as well as any potential interaction between API and excipients, such as infrared spectroscopy (IR), nuclear magnetic resonance (NMR), Raman spectroscopy, and mass spectrometry. Particularly, IR is the most used and robust technique to ensure an accurate analysis in most cases.

3.1 Fundamentals of Infrared Spectroscopy

The radiation at different regions of the electromagnetic spectrum can be used to investigate molecular processes since the basis of spectroscopy is founded on the interaction between electromagnetic radiation and matter. Thus, while microwave radiation can cause transitions between rotational energy levels of a given molecule, infrared radiation is generally associated with vibrational transitions accompanied by excitations of rotational states. Notwithstanding, ultraviolet and visible radiations (UV-VIS) can be used to investigate electronic transitions (McQuarrie and Simon 1997).

In the case of IR, a type of vibrational spectroscopy, the wavenumber range between $12,500\text{ cm}^{-1}$ and 20 cm^{-1} and can be subdivided into three subregions, namely, the far-IR ($400\text{--}20\text{ cm}^{-1}$), the mid-IR ($4000\text{--}400\text{ cm}^{-1}$), and the near-IR ($12,500\text{--}4000\text{ cm}^{-1}$) (Balan et al. 2019), as illustrated in the diagram of Fig. 7.2.

The absorbance of mid-IR radiation is associated with fundamental vibrations and related rotational-vibrational structures, such as stretching and bending modes. In the near-IR region, the absorption bands are due to overtones and combinations of fundamental vibrations (Reich 2016). On the other hand, absorptions at the far-IR region are associated with large amplitude anharmonic vibrations, such as low-frequency skeletal motions and lattice vibration of crystals, among others (Durig et al. 2017; Gilbert 2017). In this section, the attention will be directed to mid-IR spectroscopy.

The mid-IR spectra provide a unique fingerprint for each material and, therefore, have been widely used in the pharmaceutical field, especially in drug product development and manufacture (Reich 2016).

FTIR, which means Fourier-transform infrared spectroscopy, can commonly refer to an IR analysis in the mid-IR region. The Fourier transform is the basis of modern spectrometers and consists of a mathematical procedure that translates the raw acquired data (interferogram) into the spectrum. A detailed and accurate description of signal acquiring and processing can be found in the review paper of Markovich and Pidgeon (1991).

For a given vibration to be active in mid-IR, a nonzero dipole moment is necessary. When a molecule vibrates, a fluctuation in its dipole moment occurs, which causes an electric field that interacts with the electric field component of the electromagnetic radiation. Therefore, when there is a match between the natural vibration of the molecule and the frequency of radiation, the amplitude of the molecular vibration will change, and absorption will occur.

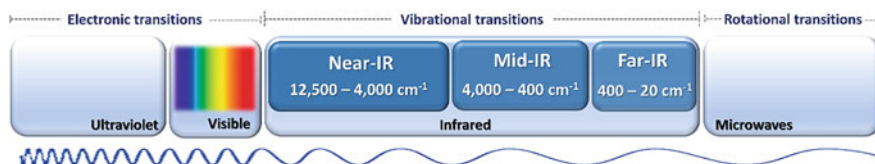


Fig. 7.2 Electromagnetic spectrum section from ultraviolet to microwaves

3.2 FTIR in Preformulation Studies

FTIR has been employed in preformulation studies as a strategy to investigate the nature of the chemical bonds and secondary interactions of specific functional groups. Thus, FTIR is a recommendable technique to verify possible critical changes caused by the processing or incompatibilities between the components that could negatively affect the drug's therapeutic action.

Often, the FTIR spectra are visually examined by the analyst in a process that involves the assignment of the main absorption bands, the analysis of the relative intensities, and the identification of the possible band shifts. Therefore, for an accurate, comprehensive, and not dispendious analysis of the spectra in a preformulation study, the following points should be considered:

- (i) *Separate the spectrum into sections.* This practice will help you to organize your interpretation. The mid-IR ($4000\text{--}400\text{ cm}^{-1}$) is usually divided into four regions, namely, the X-H stretching region ($4000\text{--}2500\text{ cm}^{-1}$), the triple-bond region ($2500\text{--}2000\text{ cm}^{-1}$), the double-bond region ($2000\text{--}1500\text{ cm}^{-1}$), and the fingerprint region ($1500\text{--}600\text{ cm}^{-1}$) (Stuart 2004).
- (ii) *Be sure what it is going to be investigated.* In the preformulation study of 3D printable dosage form, any chemical changes that could influence the performance of the pharmaceutical form for the particular intended purpose will be investigated. It includes possible thermal degradation or other undesired chemical reactions, and the possible interactions between the formulation components.
- (iii) *Have an idea of what to expect.* Before starting the analysis, one should think about the main expected absorption bands and the factors that could affect the absorption frequencies of these bands. Some factors to be considered are (a) resonance effect; (b) inter- and intramolecular interactions; (c) the presence of withdrawal and/or donor groups; and (d) hybridization, among other specific interactions that can occur in the referred system.
- (iv) *Assign the main absorption bands.* Do not expect to assign all the bands in the spectra. It is challenging to do accurately and is unnecessary. In the mid-IR, the main absorption bands are those related to the fundamental vibrations, i.e., stretching (symmetrical and asymmetrical) and bending modes (twisting, wagging, scissoring, and rocking). Nevertheless, overtones and combinations could be interesting for particular interactions. In addition, whenever possible, a deep literature search is highly recommended.
- (v) *Summarize and rationalize the observations.* The main changes observed (appearance of new bands or shoulders and widening or shifting bands) should be summarized, and then the reason for such changes should be rationalized.

Considering the specific characteristics of the studied molecular system, the results' reliability must be ensured. For example, auto-associated structures, as some carboxylic acids, may form hydrogen bonds leading to dimer structures (Thompson 2018). Therefore, the physical state and the particular characteristics of microstructure are important to be taken into account.

Within this context, a recent study used a combination of thermodynamics, IR, and quantum chemistry approaches to better understand ibuprofen's structure and molecular interaction. As the temperature increases, the C=O asymmetrical stretching at 1705 cm^{-1} decreases, while the new band absorption increases at 1746 cm^{-1} . According to the authors, this new vibrational frequency can be associated with an almost freely vibrating C=O bond since increasing the temperature could disrupt at least one of the hydrogen bonds of the cyclic dimers (Emel'yanenko et al. 2020).

In fact, this kind of analysis is a crucial and indispensable method to identify the nature of possible interactions or undesired chemical changes. Alternatively, several statistical approaches have been employed to compare FTIR spectra, either to identify a specific compound, to compare with the theoretically calculated spectrum, or to find significant changes caused by any external factor (Baumann and Clerc 1997; Henschel et al. 2020; Griffiths and Shao 2009; Pinho et al. 2021).

Pinho et al. (2021) investigated the double heating effect on the chemical nature of the formulation components. For this purpose, the authors analyzed fresh and heated physical mixtures by taking the FTIR spectra and comparing them using linear correlation in the fingerprint region of the isoniazid model drug. Correlation coefficient values close to 1 were associated with the chemical stability of the isoniazid after high-temperature processing.

The correlation coefficient is a proper technique to quantify, in a standardized way, the similarity between two arbitrary spectra by a straightforward calculation method. If the two spectra to be compared are already normalized, Pearson's product moment correlation coefficient (R) can be easily calculated by Eq. 7.1:

$$R = \frac{\sum_i (s_i - \bar{s})(r_i - \bar{r})}{\sqrt{\sum_i (s_i - \bar{s})^2} \sqrt{\sum_i (r_i - \bar{r})^2}} \quad (7.1)$$

where s and r denote the values associated with the sample and reference spectra, respectively. The two spectra must be obtained under the exact resolution and measurement conditions for this comparison.

In addition to Pearson's coefficient, which provides a measure of linear correlation between two vectors, other statistical approaches can be employed. That is the case of Spearman's correlation coefficient (ρ), described by Eq. 7.2, which measures the monotonic correlation between two vectors.

$$\rho = 1 - \frac{6 \sum_i d_i^2}{n \cdot (n^2 - 1)} \quad (7.2)$$

where d_i represents the difference between the ranks and n the number of elements. Compared with Pearson, Spearman's coefficient is generally less sensitive to outliers but can also represent nonlinear relationships (Henschel et al. 2020).

In this context, it will be helpful to use the tools reported in this section to ensure accurate and thorough analysis and interpretation of the FTIR data in a preformulation study. Nevertheless, no matter how good your FTIR analysis and interpretation, it will not be enough alone. For this purpose, complementary assays are recommended to achieve an accurate preformulation study.

4 Physical Properties

A preformulation protocol needs to consider aspects beyond chemical properties. Especially regarding a 3D printable pharmaceutical dosage form, it is necessary to draw a complete picture of the drug-excipient relationship. Moreover, it is essential to anticipate the repercussion of sample processing in possible 3D manufacturing in its physical aspects.

Within this framework, this section will focus on the formulations' thermal, mechanical, and rheological properties. In addition, the section will begin with a brief discussion of microstructural parameters that can strongly affect both the aforementioned properties and the dosage form's performance.

4.1 *Microstructure*

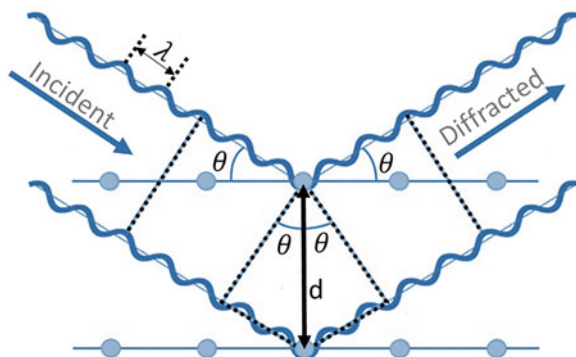
Along the processes to obtain the 3D printed pharmaceutical form, the materials suffer a variety of thermal and mechanical stresses that can strongly affect the microstructure of both filament and printed form. Thus, characteristics such as density, porosity, surface roughness, and crystalline structure, among other factors, should be considered.

During filament production by hot-melt extrusion, several imperfections may arise at the surface or inside the filament. In fact, these imperfections can represent significant drawbacks to ensuring an accurate printing process. For example, high melt viscosity can result in filaments with rough surfaces, which can cause blockages in the nozzle at the printing (Zhang et al. 2019).

On the other hand, the successive steps of melting and shearing during the whole process of hot-melt extrusion and FDM 3D printing could promote changes in the crystalline structure of the drug and excipients, including the polymer, which could exhibit a semicrystalline profile. For this reason, in the development of 3D printable pharmaceutical dosage forms, it is advisable to monitor the microstructure of materials.

X-ray diffractometry is the most common technique to evaluate the crystal structure's nature in detail.

Fig. 7.3 Atomic planes of an arbitrary crystal causing incident X-ray waves to constructive interfere. λ represents the X-ray wavelength, n is a natural number associated with the order of reflection, d is the interplanar distance, and θ is the angle of the diffraction beam



XRD is based on the diffraction phenomenon of the X-ray light by the crystalline planes formed by a highly ordered atomic distribution. This occurs due to the size of the interplanar distances that are in the order of magnitude of the X-ray wavelength. The diffraction can be successfully described by Bragg's law (Eq. 7.3).

$$n\lambda = 2d \sin \theta \quad (7.3)$$

where λ is the X-ray wavelength, n is a natural number associated with the order of reflection, d is the interplanar distance, and θ is the angle of the diffraction beam (AMEH 2019). The equation above is derived from the schematic of X-ray diffraction for constructive interference, shown in Fig. 7.3.

A crystallographic plane, or a set of planes, is vectorially described by the Miller indices notation (h , k , l) (Pecharsky and Zavalij 2009). Consequently, every diffraction peak in a diffractogram will result from a Bragg's diffraction at a specific angle 2θ from a particular family of planes (Gopirajah and Anandharamakrishnan 2019).

In the context of a preformulation study, it is necessary to consider that the heating involved in extrusion and FDM 3D printing processes could imply the recrystallization of the API inside the polymer matrix, potentially promoting the crystallization of new crystalline phases (Pinho et al. 2021). In fact, several authors have reported polymorphic phase transformations from the melting, warning of possible consequences in the bioavailability and stability of the drug product (Figueroa et al. 2022; Espinell et al. 2018; Zhang et al. 2020). In fact, polymorphism usually affects the solubility of the drug (Pudipeddi and Serajuddin 2005). In addition, the solubility of a drug in metastable polymorphic form is kinetically higher than a thermodynamically more stable polymorph (Censi and Di Martino 2015).

Furthermore, the crystallinity degree of the API is also a crucial parameter in the performance of solid dispersions. Polymers that strongly inhibit API crystallization often can maintain supersaturation (Ueda et al. 2014). Generally, amorphization of the drug represents an interesting strategy to improve poorly soluble drugs' solubility and dissolution rate (Van den Mooter 2012). In this scenario, several pharmaceutical additive manufacturing technologies are suitable for inducing the

amorphization of drugs, especially FDM 3D printing, which provides sufficient energy input to convert the drug from crystalline to amorphous state and keep it in that state for the shelf life of the drug product (Govender et al. 2021).

4.2 Thermal Properties

Thermal analyses represent a versatile set of techniques and methods that can be useful in investigating a wide variety of physicochemical properties and phenomena. Indeed, the most common choices for preformulation studies include DSC and TGA (Parulski et al. 2021). In this section, you will find a brief of the fundamentals of DSC and TGA, and some of the numerous possibilities of applications in preformulation studies, especially concerning FDM 3D printable pharmaceutical dosage forms.

(a) Differential Scanning Calorimetry

Fundamentals of DSC

A differential scanning calorimeter basically measures the difference in heat capacity between two chambers (Fig. 7.4). This is realized by monitoring the differential electrical power (ΔW) required to maintain the temperature difference between a sample and reference chambers equal to zero (Freire 1995).

In this way, if the sample experiences any thermal transition that involves heat absorption or release, or heat capacity change, a different heat flow will be needed to maintain both sample and reference in the same temperature program. These thermal

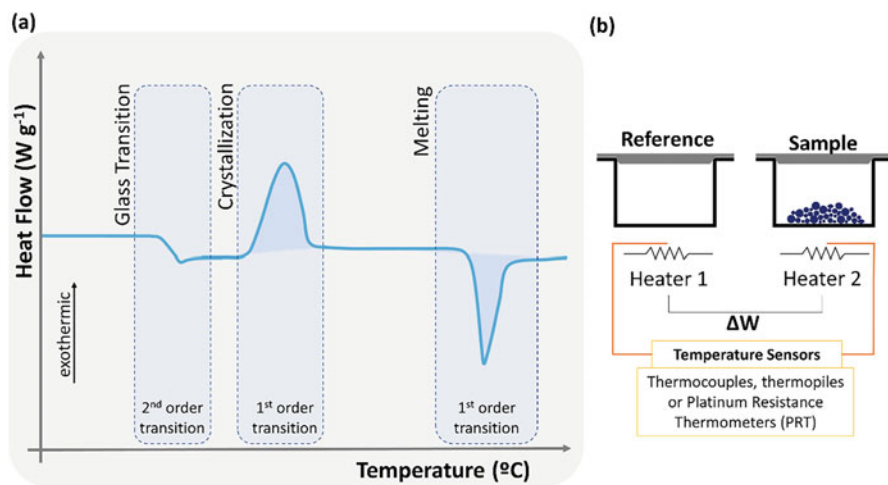


Fig. 7.4 (a) Arbitrary example of a DSC curve showing first- and second-order transitions and (b) schematic drawing of a DSC instrument

transitions are usually classified according to the Ehrenfest classification (Jaeger 1998; Leyva-Porras et al. 2019) as first- and second-order transitions.

The first-order transitions are those in which the first derivative of the chemical potential is discontinuous, i.e., characterized by a discontinuous entropy change. In turn, thermal events associated with continuous entropy change are called second-order transitions. These transitions are indicated by a discontinuity in the second derivative of the chemical potential. The thermodynamic properties that suffer a finite variation during this kind of transition include heat capacity (C_p), isothermal compressibility (β), and the coefficient of thermal expansion (α) (Leyva-Porras et al. 2019).

For example, considering a sample that suffers crystallization during a heating ramp in a spontaneous crystallization process, the entropy of the system decreases, releasing heat to the surroundings and, therefore, requiring lower heat employment from the instrument that registers the heat flow difference as an exothermic peak (Fig. 7.4a).

On the other hand, a melting process will appear as an endothermic peak (Fig. 7.4a). In this case, the heat flow required to maintain the temperature program in the sample is higher than the one required to maintain the temperature program in the reference.

As the experiments are usually realized at constant pressure, the heat involved in those processes is equal to the enthalpy change. Accordingly, the first-order transitions will always show a finite enthalpy change value resulting in a peak of the DSC curve. This enthalpy change can be easily calculated by integrating the endothermic and exothermic peaks according to Eq. 7.4 or 7.5.

Integration as a function of temperature:

$$\Delta H = \frac{1}{\tau} \int_{T_i}^{T_f} \frac{dQ}{dt} dT \quad (7.4)$$

Integration as a function of time:

$$\Delta H = \int_{t_i}^{t_f} \frac{dQ}{dt} dt \quad (7.5)$$

where dQ/dt is the heat flow and τ the modulus of the heating rate. The shaded areas in Fig. 7.4a represent those described by the integral.

The baseline depression, observed in the DSC curve for the glass transition (Fig. 7.4a), is characteristic of the heat capacity change that, as a second-order transition, is a result of thermally excitable rotations of some functional groups in the molecule.

The Role of DSC in the Preformulation Studies

Many possibilities arise regarding what to evaluate in a preformulation study. Each of them needs to be considered according to the particularities of the referred

system. Some of the most common methodologies using DSC in the preformulation step are summarized in this section.

(i) The Crystallinity of the Drug

The solubility and bioavailability of a drug vary significantly according to its degree of crystallinity. It is well known that the amorphous form has greater potential to form intermolecular hydrogen bonds, which increases its solubility in water and body fluids, especially when compared to the more stable crystalline form. In this scenario, drug amorphization is highly desired in the pharmaceutical industry, which is why various materials and processing techniques are explored in the production of pharmaceuticals, such as polymers and additive manufacturing.

Therefore, amorphization will depend on the interaction of the drug with the formulation components and the chosen processing conditions, which can be correctly selected through a preformulation study. The easiest and most common way is monitoring, often by DSC, the drug's melting in binary and/or ternary physical mixtures of drug excipients in an equal amount of the components (1,1 or 1:1:1 ratio), maximizing the possibility of visualizing an eventual phenomenon (Oliveira et al. 2009; Alencar et al. 2022). However, in the case of 3D FDM, for example, the materials are first extruded by HME before printing. Thus, for multiprocessing 3D techniques, a worthwhile protocol would be to evaluate the drug's crystallinity in the intermediate drug product (polymeric filament) by selecting the formulation components.

The crystallinity degree (X_c) can be determined by Eq. 7.6, in which $\Delta_m H$ is the melting enthalpy change; $\Delta_c H$ is the crystallization enthalpy change; $\Delta_m H^\circ$ is the melting enthalpy change of 100% crystalline drug; and f_{drug} is the mass fraction of the drug in the sample (Dreyer et al. 2020).

$$X_c = \frac{\Delta_m H - \Delta_c H}{\Delta_m H^\circ \cdot f_{drug}} \quad (7.6)$$

Prasad et al. (2019) produced filaments with HPMC and paracetamol in different concentrations. The drug's melting temperature and enthalpy were evaluated and compared with filament printability. It was observed that not only the degree of amorphization influences the 3D printing but also the amount of amorphous material present in the filament, for example, a scenario in which 40% of the amorphous drug in the filament may not be interesting, as it can change its mechanical and rheological properties to prevent the printing step.

(ii) Drug-Polymer Interaction

The drug-polymer interaction is crucial to guarantee all the physical-chemical changes mentioned in this chapter, such as the drug's dispersion in the matrix, polymer plasticization, and mechanical and rheological modifications. In this way, determining the drug-polymer interaction is decisive within a preformulation study and can be performed using the Flory–Huggins parameter (Tian et al. 2013).

The Flory–Huggins parameter (χ) is a dimensionless quantity that evaluates the differences in the strength of pairwise interaction energies between molecular entities, e.g., polymer and drug (Kozuch et al. 2016). Therefore, this theory, along with the melting point depression assessed by DSC analysis, can be used to predict the solubility and miscibility of the drug in a polymer by the Eq. 7.7:

$$\frac{1}{T_m} - \frac{1}{T_m^0} = -\frac{R}{\Delta H} \left[\ln \phi_{\text{drug}} + \left(1 - \frac{1}{m}\right) \phi_{\text{poly}} + \chi_{\text{drug-poly}} \phi_{\text{poly}}^2 \right] \quad (7.7)$$

where T_m and T_m^0 are the melting points of the drug in the drug/polymer mixture and the pure drug, respectively; R is the gas constant; ΔH is the heat of the drug melting event; and ϕ is the volume fraction of the drug.

This approach was explored by Tian et al. (2013) that used Flory–Huggins theory to determine the χ parameter conjointly with DSC data. This evaluation was important to predict the miscibility of the drug felodipine in two different pharmaceutical polymers (HPMC-AS and Soluplus[®]) and compare the systems in order to evaluate which one would be the best composition to form an amorphous and stable solid dispersion.

(iii) Polymer Plasticization

The vast majority of polymers available on the market, especially pharmaceuticals, are not developed for the 3D market since these materials are usually rigid and brittle (Lima et al. 2022). This scenario is even worse for the polymeric filaments used in FDM 3D printing, as this technique requires more malleable materials.

The intermolecular interactions between the polymer and other components, such as plasticizer and drug, modify the molecular mobility of the polymer chain by decreasing the intramolecular polymer-polymer interactions – polymer plasticization (Llanes et al. 2021; Enumo et al. 2020). Thus, with the proper processing conditions in the right composition and ratio, most pharmaceutical polymers can have their physical properties modulated, making them printable.

The increase in polymer chain mobility leads to a decrease in the glass transition temperature (T_g). Hence, identifying and monitoring T_g in different circumstances are advisable to evaluate the plasticizing effect. Thus, a screening study of different materials under various processing conditions can provide valuable information in a preformulation protocol, such as when the association of the materials leads to a decrease in T_g and, consequently, an increase in filament malleability.

The glass transition is a change in heat capacity (second-order phase transition). Hence, there is no change in enthalpy. Therefore, in a DSC analysis, the T_g is identified by a drop in the baseline, and the evaluation procedure is described in ASTM E1356-08, 2014.

A study with the polymer Soluplus[®] and different plasticizers (triethyl citrate, citric acid, and polyethylene glycol) evaluates the miscibility of the plasticizer in the polymer suitable for HME. The T_g results evaluated by DSC, together with the other analyses of the screening protocol, helped to define which samples would promote a suitable filament in HME in terms of miscibility and malleability (Barmplexis et al. 2018).

(b) Thermogravimetric Analysis

TGA is a simple technique obtained using a highly sensitive thermobalance in which a sample can be submitted to various customized temperature programs under a controlled atmosphere.

It is important to emphasize that physical or chemical processes that involve the release of gaseous substances will not be distinguishable. Therefore, the nature of the phenomena that caused the mass loss needs to be carefully understood and reasoned before arbitrarily attributing causes. In this context, some studies have also used TGA coupled with other analytic techniques, such as TGA-coupled-FTIR, TGA-coupled-GC, or TGA-coupled-MS, to investigate the chemical nature of the released gaseous substances (Kasprzyk et al. 2020; Wojtyła et al. 2017; Wojnowski et al. 2022).

In the context of the preformulation studies, it is common to make a comparative analysis between the pure compounds, the physical mixtures, and the processed ones. Considering a homogeneous dispersion and representative sample, if there is no interaction between the components able to change the thermal degradation mechanism, the result observed for the mixtures should be just a linear combination of the results for pure compounds.

In this way, a theoretical curve for a system with N components can be constructed (Daniel et al. 2020; Pinho et al. 2021) by calculating each predicted mass percent value at a temperature T ($m(T)$) from Eq. 7.8.

$$m(T) = \sum_i^N x_i \cdot m_i(T) \quad (7.8)$$

where x_i represents the mass fraction of the component “ i ” in the mixture and $m_i(T)$ the mass percent value of the pure component “ i ” at a temperature T . The resulting theoretical curve $m(T)$ versus T will be the initial parameter for comparison.

If the thermal degradation mechanism is changed, the activation energy of the process will probably also be changed. Therefore, to investigate it thoroughly, the activation energy can be both isothermally and non-isothermally determined by TGA.

Alves-Silva et al. (2014) and Pinho et al. (2021) have performed isothermal experiments to determine the activation energy (E_a) of thermal degradation, plotting the obtained data according to the Arrhenius equation (Eq. 7.9):

$$k(T) = A \exp(-E_a/RT) \quad (7.9)$$

However, alternative non-isothermal approaches have been used. That is the case of some well-known non-isothermal kinetics methods, including Friedman, Flynn-Wall-Ozawa, Coats-Redfern, and Kissinger equations (Sun et al. 2020). Most of these models involve the time-dependent Arrhenius equation (Eq. 7.10).

$$d\alpha/dt = A \exp(-E/RT) f(\alpha) \quad (7.10)$$

That can be rewritten by considering that the heating rate is given by $\beta = dT/dt$:

$$d\alpha/dT = (A/\beta) \exp(-E/RT) f(\alpha) \quad (7.11)$$

where α is the weight conversion degree, A is the pre-exponential factor, E is the apparent activation energy, R is the general gas constant, T is the absolute temperature, and $f(\alpha)$ is the reaction model, which depends on the reaction mechanism (Sun et al. 2020).

In short, it is possible to conclude that the TGA is a useful tool to understand better whether the interaction between the components can affect the thermal degradation reaction mechanism and, therefore, the thermal stability of the sample.

In addition, the TGA results could provide almost enough information to set the hot-melt extrusion and printing parameters to avoid undesirable thermal degradation or volatilization of small molecules from the bulk of the polymer matrix.

4.3 Mechanical and Rheological Properties

Mechanical and rheological properties of the polymeric “ink” can strongly affect the printing process. Particularly in the case of FDM 3D printing, the filament experiences two sequential stages of thermomechanical stress in the feeding and the melting zones.

In the first stage, a mechanical gearing arrangement in the feeding zone is needed to push the filament into the heating zone. Next, the melted material in the heating zone needs to be adequately extruded to ensure the continuity of the process.

This means that the filament cannot be so soft as to suffer a compromising irreversible deformation or bending (Fig. 7.5a) or so brittle that it can break during the tension in the feed (Fig. 7.5b) (Zhang et al. 2017; Awad et al. 2018). On the other hand, in the melting zone, the material cannot be too fluid that it affects the layer thickness control in the 3D construction process (Fig. 7.5d), nor so viscous as to make it difficult to flow through the nozzle (Fig. 7.5e).

Therefore, print quality assurance is associated with the ideal scenario illustrated by Fig. 7.5c, f, which involves specific mechanical and rheological properties under particular printing conditions.

The most common pharmaceutical polymer grades suitable for hot-melt extrusion often yield brittle and fragile materials. This is probably because its characteristic is directed based on the requirements for traditional pharmaceutical applications that involve obtaining granules and tablets by compression (Nasereddin et al. 2018).

To better adapt pharmaceutical materials to additive manufacturing, the most common strategy has been the addition of plasticizers, as discussed before. However, the choice of the plasticizer, as well as the amount used, is crucial to achieving

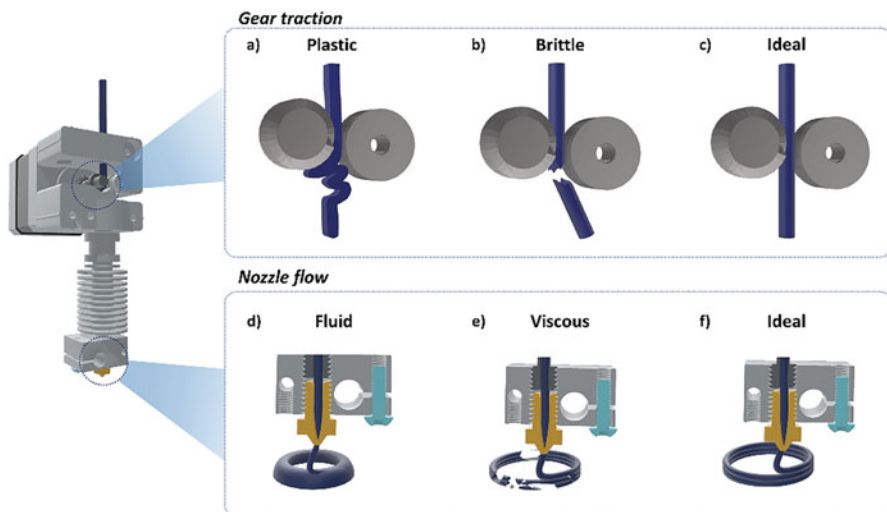


Fig. 7.5 Schematic drawing of how filaments' mechanical and rheological properties can affect the printing processing during gear traction (a–c) and nozzle flow (d–f). (a) Too soft, (b) too brittle, (c) ideal behavior, (d) too fluid, (e) too viscous, and (f) ideal behavior

the required properties. Indeed, overplasticization can lead to undesired situations, such as excessive filament flexibility (Awad et al. 2018).

Polymeric materials often exhibit a mechanical behavior that is not purely elastic or plastic but viscoelastic. Therefore, some properties concerning to elastic and plastic characteristics of the filament and printed materials can be studied by employing static or dynamic mechanical analyses.

Tensile tests are the simplest way to investigate properties such as Young's modulus, yield strength, and fracture, as illustrated in Fig. 7.6. Such tests can be performed in a universal testing machine or dynamic mechanical analyzers equipped with a tension clamp. Often, the equipment allows the data to be registered as force or stress. To manually convert force data into stress, just divide the force by the transversal area of the cylinder specimens, in the case of the filaments, as highlighted in Fig. 7.6.

Young's modulus provides information about how much stress must be employed on the material to cause a reversible deformation. It consists of the ratio between the stress and dimensionless strain and is determined as the slope of the linear section of the stress-strain curve (Fig. 7.6).

When the elastic region is not well defined, the determination of the secant modulus is indicated. According to ASTM D5323 – 92 (2018), the secant modulus is usually lower than Young's modulus and is estimated by the slope of the secant line that intersects the stress-strain curve at the origin and 2.0% of strain. In these cases, the yield strength can also be challenging to determine. For this reason, an arbitrary offset yield strength is often calculated using 0.2% strain.

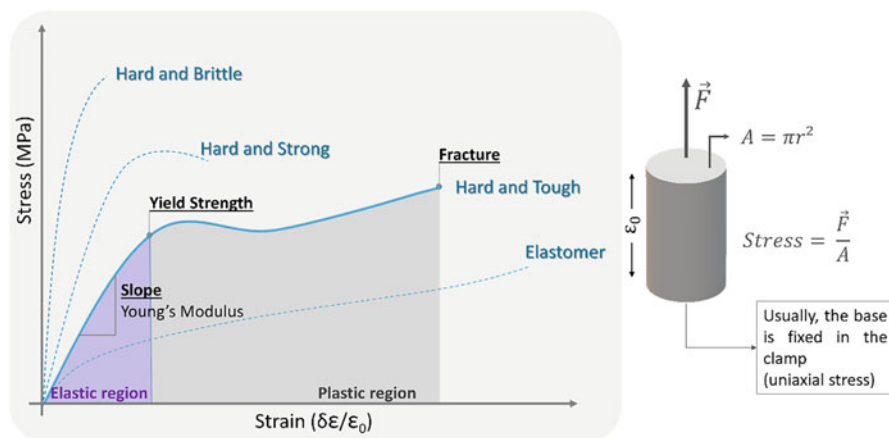


Fig. 7.6 Stress-strain curves obtained from tensile tests illustrating different mechanical behaviors for arbitrary samples, together with a scheme of a specimen in the form of a cylinder filament, where $\vec{F}$ is the applied force, A is the area perpendicular to the force, r is the radius of the filament, and ϵ_0 is the length of the specimen at initial time, before any force employment

Another important mechanical property in developing a 3D printable dosage form is the breaking stress, marked in Fig. 7.6 as the fracture point. Filaments with breaking stress higher than 8.5 MPa have been described as capable of supporting the traction employed by an FDM 3D printer (Yang et al. 2021). Generally, the best materials for FDM 3D printing are those classified as hard and tough or hard and strong materials, whose typical mechanical behavior is shown in Fig. 7.6. Therefore, the mechanical properties become crucial to determine the feedability of a filament. However, to elucidate its printability, the rheological properties are the most suitable, which can be accessed with dynamic measurements.

Dynamic rheological measurement is mostly performed with two equipments: a mechanical dynamic analyzer (DMA) and an oscillatory rheometer. This technique is based on the viscoelasticity theory, which ties the concept of elasticity and viscosity proposed in Hooke's and Newton's law, respectively (Sheng 2011). For Hookean solids, the stress is directly proportional to strain in deformations and is not dependent on strain rate. In turn, for Newtonian liquids, the stress is directly proportional to the strain rate and is not dependent on the strain (Murata 2012). As previously explained, polymers exhibit viscoelastic behavior, i.e., a nonconstant and nonproportional stress-strain response with time- and temperature-dependent behavior.

Figure 7.7 represents an illustrative adaptation of the coordinate system proposed by Eizenschitz in 1929, which expose the different energetic phenomena (kinetic energy; energy conservation; energy dissipation) exerted by materials in a rheological event and the variation of its viscoelastic behavior (Mezger, 2014). For this reason, deformations that involve energy storage are associated with a storage modulus, also called the elastic modulus (G' or E'). On the other hand, deformations

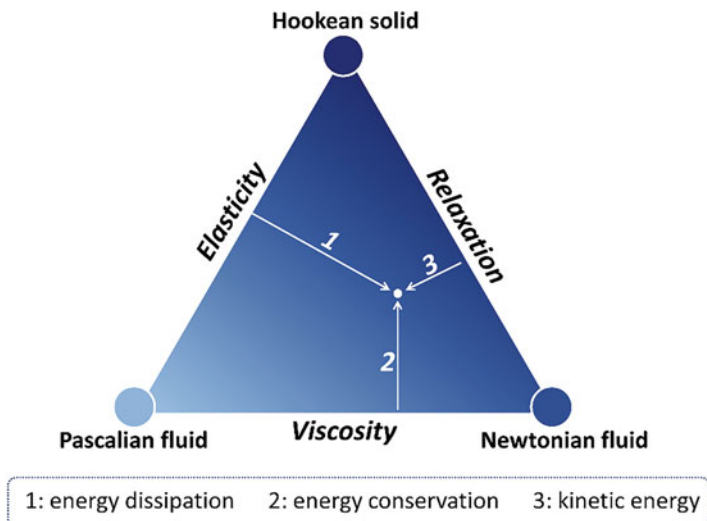


Fig. 7.7 Illustrative adaptation of the coordinate system proposed by Eizenschitz in 1929, indicating energy variations (dissipation, conservation, and kinetics) along the behavior of a viscoelastic material

associated with energy release are represented by a loss modulus, also called the viscous modulus (G'' or E'') (Sheng 2011).

The terminology “ G ” or “ E ” varies depending on the nature of the stress applied to the material. For example, when tension stress is exerted to measure the moduli, the nomenclature E' and E'' are used. On the other hand, when shear stress is applied, G' and G'' are used (ASTM D4092-21, 2021). This is due to the fact that the DMA employs normal forces over the specimens while the rheometer employs a shearing force.

Figure 7.8 illustrates stress and strain variations with time in a dynamic experiment. The lag between the peak of each wave is called phase angle delta (δ), which is $\delta = 0$ rad for ideally elastic materials (Fig. 7.8a), $\delta = \pi/2$ rad for ideally viscous materials (Fig. 7.8b), and $0 \text{ rad} < \delta < \pi/2$ rad for viscoelastic materials (Fig. 7.8c).

Therefore, the dynamic tension and shear moduli are defined by the following equations:

$$E' = \frac{\sigma_0}{\epsilon_0} \cos \delta \quad \text{or} \quad G' = \frac{\tau_0}{\gamma_0} \cos \delta \quad (7.12)$$

$$E'' = \frac{\sigma_0}{\epsilon_0} \sin \delta \quad \text{or} \quad G'' = \frac{\tau_0}{\gamma_0} \sin \delta \quad (7.13)$$

Moreover, another important variable for the characterization of polymeric materials is the $\tan \delta$, which is the ratio of energy lost and energy stored, defined by

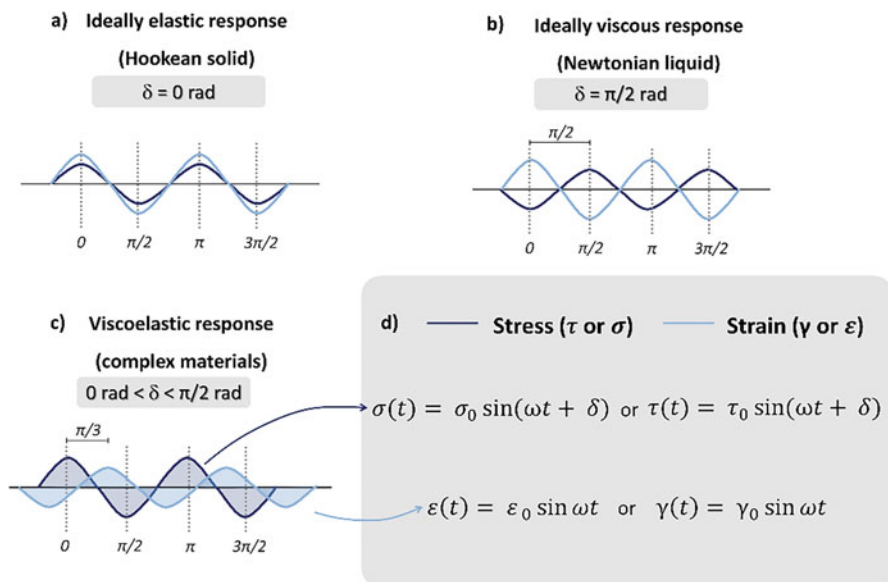


Fig. 7.8 Sinusoidal stress-strain curve with a representation of the phase angle (δ) for the deformation of a hypothetical material (a) purely elastic, (b) purely viscous, and (c) viscoelastic. Dark blue curves represent the stress (σ) and the light blue the strain (γ or ε). (d) The equations for determining stress and strain are represented in a case where strain is applied and stress is measured; ω is the frequency of strain oscillation, and t is the time

Eq. 7.14 (Mezger, 2014). The higher the value of $\tan \delta$, the greater the potential for energy dissipation of the material. Hence, it is crucial to discuss the polymer's macromolecular mobility.

$$\tan \delta = \frac{E''}{E'} \quad \text{or} \quad \tan \delta = \frac{G''}{G'} \quad (7.14)$$

Among the various analyses that can be performed in DMA and rheometer, the temperature ramp is the most applied. As the DMA is mainly used to analyze solid samples, the rheological properties are determined before the materials melt. On the other hand, the rheometer operates with liquid-like samples. Thus, the rheological properties are obtained in temperature regions near materials melting (Fig. 7.9).

In this scenario, several publications explored the temperature ramp test performed in a DMA to measure the E'' and E' moduli of polymeric filaments below the rubbery state. Furthermore, the determination of the glass transition could be obtained through the onset of the $\log E'$ curve (ASTM D7028 – 07, 2015). In fact, DMA analysis is more sensitive for such second-order transition when compared to DSC; thus, the determination of T_g by DMA is more reliable (Xiao et al. 2020).

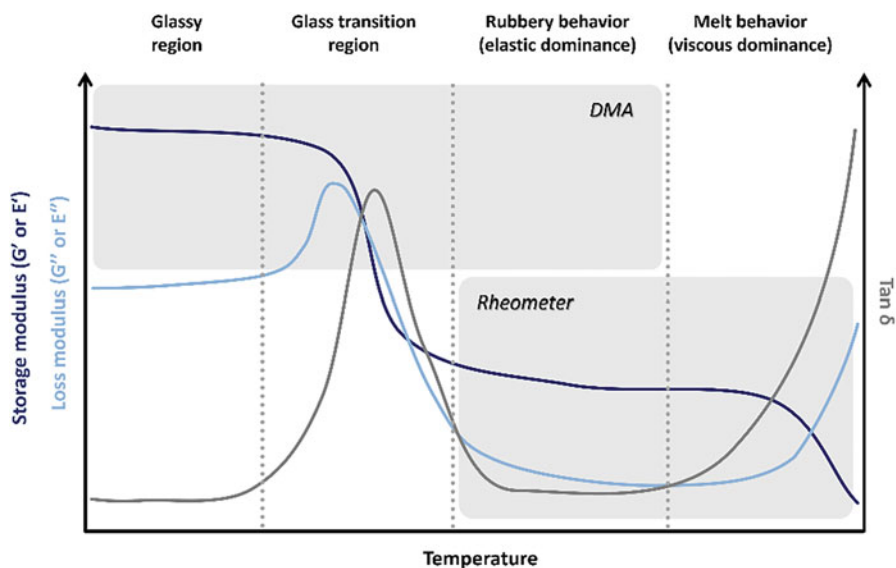


Fig. 7.9 Temperature ramp performed by dynamic rheological test. The different rheological deformation regions are defined (glassy, glass transition, rubbery, and melt region), along with the temperature and deformation range in which a dynamic mechanical analyzer and a rheometer can operate

For rheometry, in turn, a preformulation study for 3D printing pharmaceuticals, Pinho et al. (2021) performed temperature ramp analysis of physical mixtures of different polymers and isoniazid, aiming the evaluation of molten viscosity at different temperatures in order to choose the ideal processing thermal zone. Moreover, another study carried out the same analysis for poly(vinyl alcohol) filaments by melting the material in the equipment and observing different rheological properties with increasing temperature to determine which would provide better printability (Lima et al. 2022).

Therefore, DMA and rheometer must be used in a preformulation protocol since both are complementary techniques, enabling the analysis of the polymeric filament in different physical states, consistent with the different unit operations present in FDM 3D printing process, i.e., filament feeding step (solid material) and 3D object construction (molten material).

5 Designing a Preformulation Study

In order to outline a comprehensive protocol through which a preformulation study of 3D printable pharmaceutical dosage forms could be performed, a five-step flowchart is proposed in Fig. 7.10. Some questions permeate all the steps to direct the actions to be taken in each particular moment of the preformulation study.

Step 1: Selecting the Starting Materials

The first step is decisive for the success of the entire preformulation study and is often performed theoretically by analyzing the information available in the literature. In this step, the materials must be chosen, at least considering (i) the processing; (ii) compatibility and interaction between the components; (iii) solubility; and (iv) other specific properties required for the performance of the intended dosage form. The materials chosen must be able to go through all the expected processing steps. For the FDM technique, for example, both the API and the excipients must be stable under the range of prospected processing conditions.

Next, the interaction between the selected compounds must be considered and can be predicted based on their solubility parameters. This strategy is a valuable tool,

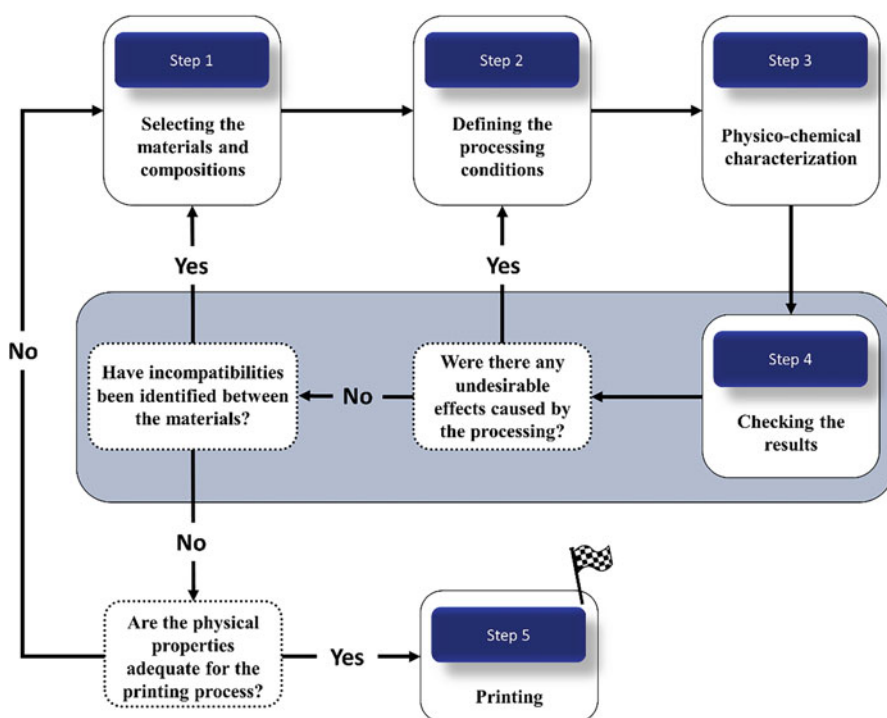


Fig. 7.10 Process flowchart to guide preformulation studies of 3D printable pharmaceutical dosage forms

and the data can be found in the literature for commonly used material, experimentally determined, or calculated by the method of Hoftyzer and van Krevelen (1976), for example (van Krevelen and Nijenhuis 2009). This theoretical approach allows the calculation of the solubility parameter considering the contribution of the material's structural groups, including contributions such as dispersive (Eq. 7.15), polar (Eq. 7.16), and hydrogen bonding (Eq. 7.17) of polymers, drug, and other excipients.

$$\delta_d = \frac{\sum F_{di}}{V} \quad (7.15)$$

$$\delta_p = a \frac{\sum F_{pi}^2}{V} \quad (7.16)$$

$$\delta_h = \sqrt{\frac{\sum F_{hi}}{V}} \quad (7.17)$$

where δ_d is the component of dispersive forces; F_{di} is the group contribution to the dispersive forces; δ_p is the component of polar group forces; F_{pi} is the plane symmetry factor of polar groups; δ_h is the component of hydrogen bond energy; F_{hi} is the group contribution to hydrogen bonding energy; and V is the molar volume (van Krevelen and Nijenhuis 2009).

Then, these components can be correlated to provide a molecule's overall solubility parameter through a vector sum (Eq. 7.18).

$$\delta_T = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \quad (7.18)$$

Moreover, the group contribution method proposed by Hoftyzer and van Krevelen can estimate the Flory–Huggins parameter (χ) (explained in topic 7.4.2) using Eq. 7.19. In practice, when the $\delta_{\text{drug}} - \delta_{\text{polymer}}$ tends to zero, the interaction between drug and polymer is favorable.

$$\chi = \frac{V_0}{RT} (\delta_{\text{drug}} - \delta_{\text{polymer}})^2 \quad (7.19)$$

Hence, these models explore physical-chemistry fundamentals to theoretically estimate the solubility of a drug in a polymer matrix. In this sense, it is possible to obtain information on materials miscibility, which is essential for producing a pharmaceutical product with suitable performance.

Step 2: Defining the Processing Conditions

As most 3D printing techniques use high temperatures, it is crucial to investigate pure compounds' degradation and/or volatilization to define the appropriate processing conditions. This step is crucial for formulations that undergo more than one heating process, as in the case of FDM 3D printing, in which the material is first extruded at high temperatures to form a filament that will be heated again to even higher temperatures when fed into the 3D printer.

In this scenario, the TGA technique (explained in topic 7.4.2) is ideal for this type of evaluation since it allows identifying the initial temperatures of degradation and evaporation, as well as understanding its kinetics process. For this, samples of the drug and excipients must be analyzed separately and combined in a physical mixture. After this step, it will be possible to select a temperature range that potentially represents thermal stability for the formulation.

To ensure adequate flow and good miscibility of the components in the extruder at a specific temperature, it is important to know the melting temperature and the glass transition of the drug and the polymer. Furthermore, considering that the extrudate has different physicochemical properties from the material as supplied, these same thermal properties must be measured for the filament in order to assist in the temperature chosen for printing. These analyses can be performed through the DSC, as described in topic 7.4.2.

Moreover, the rheology of the molten material is also important for the choice of the processing temperature, as it is a dominant condition for the melt viscosity of the material. Hence, although the limited number of works with this type of analysis in the preformulation of 3D printable structures, the determination of the rheological properties of the molten filament (described in topic 7.4.3) is decisive in obtaining printable materials.

Step 3: Physicochemical Characterization

The physicochemical characterization of the materials along all the steps to obtain a 3D printable pharmaceutical dosage form is essential for a preformulation study. Any wrong choice or decision made in the previous steps will be detected and better understood through appropriate physicochemical screening.

As discussed in this chapter, a proper preformulation study involves physical and chemical characterization combining several techniques. Some of them were discussed in the previous sections, namely, (i) infrared spectroscopy; (ii) X-ray diffraction; (iii) differential scanning calorimetry; (iv) thermogravimetric analysis; (v) tensile tests; (vi) dynamic mechanical analysis; and (vii) oscillatory rheometry.

However, it is important to emphasize that the choice of techniques needs to be carried out considering the system's particularities and the nature of the property or phenomenon to be studied. For this reason, the techniques presented here cannot be considered a closed protocol that will work for any case.

It is crucial to remember that the main objective when developing a preformulation study is to ensure that no undesirable physical or chemical changes will make the dosage form unfeasible. For this purpose, a compilation of several techniques used in preformulation screenings, especially those involving melt processing of the materials, are presented together with some references in Table 7.1. In this context, an experimental design could be proposed considering the specific objectives described in the first column of Table 7.1.

Step 4: Checking the Results

When performing the physicochemical characterization, the results must be accurately analyzed, and the conclusions are summarized based on three critical questions:

- (a) Were there any undesirable effects caused by the processing?
- (b) Have incompatibilities been identified between the materials?
- (c) Are the physical properties adequate for the printing process?

Note that these questions are not intended to guide all the data interpretation and results. It is just a check step and should not limit all the vast and rich interpretations constructed with the obtained results. It aims to screen the main problems that could affect the performance of the pharmaceutical form, making it unfeasible.

Therefore, the answer to each of these questions leads to different results that imply going back to some previous steps or continuing to the printing process, as described in Fig. 7.10. After following all the steps described in this topic, the selected materials can be printed. Moreover, the characterization and performance evaluation analysis of the 3D pharmaceutical dosage form can be performed to follow the study.

Table 7.1 Compilation of some reported techniques used in preformulation screenings, especially those involving melt processing

Objective	Possible techniques	References
Evaluate the chemical stability of the materials to the processing conditions	Chromatographic techniques (HPLC, GC, GPC)	Haser et al. (2017a, b), Follonier et al. (1995) and Kollaraman et al. (2018)
	Fourier-transform infrared spectroscopy (FTIR)	Silva et al. (2022), Liaskoni et al. (2021), Figueiredo et al. (2021) and Pinho et al. (2021)
	TGA, TGA-co-FTIR, TGA-co-MS	Liu et al. (2011) and Tudorachi and Chiriac (2011)
Evaluate the physical properties	<i>Microstructure</i> X-ray diffractometry (XRD) Hot-stage microscopy (HSM) Scanning electron microscopy (SEM) Atomic force microscopy (AFM)	Silva et al. (2022), Than and Titapiwatanakun (2021), Verstraete et al. (2018), Liaskoni et al. (2021), Liu et al. (2011) and Pinho et al. (2021)

(continued)

Table 7.1 (continued)

Objective	Possible techniques	References
	<i>Mechanical and rheological behavior</i> Tensile tests of filaments Dynamic mechanical analysis (DMA) Oscillatory rheometry	Samaro et al. (2020), Yang et al. (2021); Xu et al. (2020) and Boetker et al. (2016)
	<i>Thermal properties</i> Differential scanning calorimetry (DSC) Thermogravimetric analysis (TGA) Modulated DSC (MDSC)	Genina et al. (2016); Cui et al. (2020), Tan et al. (2019), Patel and Serajuddin (2021) and Tabriz et al. (2021)
Investigate the drug-excipient interaction	Hansen solubility parameters (HSP)	Haser et al. (2017a), Forster et al. (2001), Sarode et al. (2013) and Maniruzzaman et al. (2013)
	Fourier-transform infrared spectroscopy (FTIR)	Haser et al. (2017b), Liu et al. (2011), Scoutaris et al. (2018) and Than and Titapiwatanakun (2021)
	Near-infrared spectroscopy (NIR)	Saerens et al. (2012) and Islam et al. (2015)
	X-ray photon spectroscopy (XPS)	Maniruzzaman et al. (2013)
	Raman spectroscopy	Renterghem et al. (2017), Crisan et al. (2021) and Scoutaris et al. (2018)
	Nuclear magnetic resonance (NMR)	Kollaraman et al. (2018), Haser et al. (2017b) and Wu and McGinity (2003)

6 Conclusions

Since 3D printing emerged as a promising pharmaceutical technology technique, an adapted preformulation protocol is an important issue to be discussed. In this chapter, a broad explanation of the main characterization techniques involved in this kind of study helps propose a basic preformulation protocol for developing 3D printable pharmaceutical dosage forms. This protocol is not limited to the techniques discussed. Still, it is based on evaluating the physical and chemical properties of the components and mixtures during each step of the process, aiming to guarantee the integrity of the components, the success of the printing, and the performance of the drug product.

Multiple Choice Questions

- Ibuprofen melts around 75 °C, and its melting enthalpy change is 26 kJ mol⁻¹. In order to prepare an FDM 3D printing filament, poly (vinyl alcohol), ibuprofen, and glycerol are extruded in the weight proportion of 70/20/10. A DSC analysis of the filament shows an endothermic peak at 73 °C with an enthalpy change of 12.6 J g⁻¹, and no cold crystallization peaks were observed. Supposing neither component suffers any degradation or volatilization at the process conditions, calculate the crystallinity degree of the ibuprofen in this sample (molar weight ibuprofen = 206.3 g mol⁻¹).
(a) 10% (b) 12.6% (c) **50%** (d) 48.5% (e) 20%
- Suppose that in question 1, pure ibuprofen shows a C=O band, characteristic of carbonyl stretching of ibuprofen cyclic dimer (confirmed by XRD), at 1710 cm⁻¹. However, this band disappears in the filaments produced, and a shoulder is observed at 1727 cm⁻¹. Over time (days, weeks, and months), the band at 1710 cm⁻¹ appears again and becomes more intense with time, while the shoulder at 1727 cm⁻¹ becomes less intense. Choose the alternative that corresponds to the more plausible explanation.
(a) The ibuprofen degraded by decarboxylation
(b) ***The dimer structure has broken by the dissolution of ibuprofen crystal in the polymer matrix***
(c) Ibuprofen was esterified by glycerol
(d) Poly(vinyl alcohol) was grafted by ibuprofen in an esterification reaction
- Suppose that you must choose the plasticizer and drug most prone to interact with a certain polymer matrix with a $\delta_T = 21.9 \text{ MPa}^{1/2}$. Select the most appropriate pair of plasticizer and drug (all values shown are in MPa^{1/2}).
(a) Triethyl citrate ($\delta_d = 16.5$, $\delta_p = 4.9$, $\delta_H = 12.0$) and theophylline ($\delta_T = 28.1$)
(b) Glycerol ($\delta_d = 17.4$, $\delta_p = 12.1$, $\delta_H = 29.3$) and theophylline ($\delta_T = 28.1$)
(c) Glycerol ($\delta_d = 17.4$, $\delta_p = 12.1$, $\delta_H = 29.3$) and paracetamol ($\delta_d = 17.8$, $\delta_p = 10.5$, $\delta_H = 13.9$)
(d) ***Triethyl citrate ($\delta_d = 16.5$, $\delta_p = 4.9$, $\delta_H = 12.0$) and paracetamol ($\delta_d = 17.8$, $\delta_p = 10.5$, $\delta_H = 13.9$)***

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Chapter 8

Vat Photopolymerization Methods for Drug Delivery Applications



Giulia Pitzanti and Dimitrios A. Lamprou

Abstract Vat photopolymerization (VP) is a family of 3D printing (3DP) technologies based on the photopolymerization of liquid light curable resins. VP 3D printed drug delivery systems (DDSs) have gained increasing popularity, offering multiple advantages over traditional DDS. Among them they offer the possibility to manufacture 3D devices with customizable design and intricate structure, and centred to the patient needs, facilitating the personalized medication. This chapter describes the VP techniques used for drug delivery applications, their advantages and limitations, and an overview of the DDS manufactured with VP 3DP technology.

Keywords Three-dimensional printing · Vat photopolymerization · SLA · DLP · LCD · CLIP · TPP · Tablets · Microneedles · Implants

1 Introduction

The term vat photopolymerization (VP) is commonly used to designate a group of 3D printing (3DP) technologies which apply the photopolymerization process. VP utilizes computer-spatially controlled photopolymerization to selectively harden liquid light curable resins located into a vat and manufacture solid objects. Liquid light curable resins for VP are commonly composed by three elements: monomers, oligomers, and photoinitiators. During VP, the light curable resin is placed into a vat and exposed to the action of visible or UV light. The exposure to the curing light activates the photoinitiator forming reactive species that catalyse the chain formation between monomers and oligomers. The resin state changes from liquid to solid (Fig. 8.1). The photopolymerization process is irreversible, and there is no way to convert the 3DP parts back to their liquid form (Pagac et al. 2021).

VP 3DP process takes place in three main steps. The first step is named pre-processing. Similarly, to other 3DP technologies, VP requires three-dimensional

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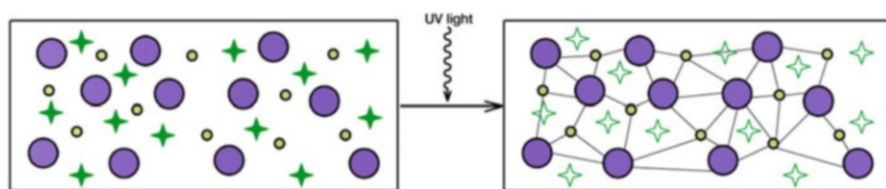


Fig. 8.1 Liquid light curable resin (on the left) and induced polymerization by UV light (on the left) (small circle-monomer, large circle-oligomer, star-photoinitiator). (Reproduced from Pagac et al. 2021)

models to create physical objects. These can be designed with a computer-aided design (CAD) software or obtained by using imaging techniques that take instantaneous images, for example, of the anatomical parts of a patient using a magnetic resonance imaging (MRI) scan. Three-dimensional models are then transformed into the standard triangulation language (.STL) format. In the printer software, the orientation in the building platform and the supports are optimized. Finally, the STL model is sliced into layers by the printer software. Pre-processing is followed by processing. During this stage, the printer light source determines the curing of the liquid photopolymer resin stored into a vat. The process proceeds until the 3D object is completed.

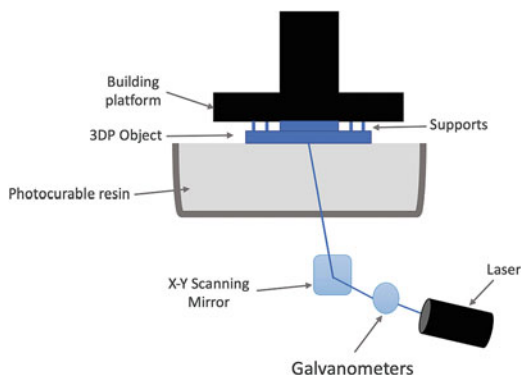
Finally, the 3DP part is post-processed. During this step, the 3DP part is washed usually with isopropyl alcohol (IPA) to remove any excess of resin that has not polymerized. After that, it is cured with UV light or sunlight in order to ameliorate its mechanical properties. Additional post-processing operations include support removal, grinding, sealing, gluing, polishing, painting, varnishing, coating, sterilization, inspection, and measurement (Pagac et al. 2021).

The most common VP processes used in drug delivery include stereolithography (SLA), digital light processing (DLP), ultraviolet (UV) liquid crystal display (LCD), continuous liquid interface production (CLIP), and two-photon polymerization (TPP).

2 Stereolithography (SLA)

SLA is considered the oldest additive manufacturing (AM) technique. Indeed, the first appearance of this 3DP technology dates to the early 1970s, when Japanese researcher Dr. Hideo Kodama invented the first SLA device that uses ultraviolet light to cure photosensitive polymers and create 3D objects (Hagiwara 2001). However, it was only few years later in 1986 that Charles Hull patented the technology and founded the company 3D Systems to commercialize it. Hull reported the method as building three-dimensional objects by successively creating thin laminae of a fluid material curable by ultraviolet light, one on top of the other (Hull 1986).

Fig. 8.2 Schematic representation of an SLA 3DP process



An SLA 3D printer is constituted by the following parts (Fig. 8.2):

- A tank which contains the liquid photocurable resin.
- A platform which can be lowered into the resin tank and can move up and down along the Z-direction. The 3D object will be built in this part of the printer.
- An ultraviolet laser.
- A galvanometer system which uses an X-Y motorized scanning mirror to direct the laser beam on the resin allowing to trace the geometry of the design (Huang et al. 2020).

How Does Stereolithography Work?

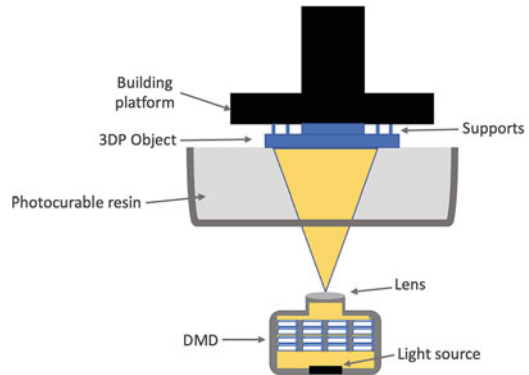
After the CAD is transferred into the 3DP software, the stereolithography printing process follows the next steps:

- Step 1: The building platform is dipped into the resin tank at a distance from the bottom of the tank corresponding to the height of one layer. The UV laser is activated and is directed by the X-Y scanning mirror on the resin, drawing and solidifying the first layer of the model.
- Step 2: After the first layer is completed, the platform is raised according to the layer thickness and additional resin flows below the already printed layer. The laser then solidifies the following layer, and the process is repeated until the whole part is complete.
- Step 3: After finishing the part, the platform rises out of the resin tank; the model is removed from the platform and washed of excess resin with alcohol, and support structures are removed.
- Step 4: The model is then placed in a UV oven for final curing in order to reach the highest possible strength and become more stable (Vaz and Kumar 2021).

Advantages and Limitations

Stereolithography is considered as one of the most precise 3DP technologies available on the market. Indeed, it can create parts with very high quality, highly detailed features and complex shapes. Layer thicknesses can be made as low as 25 μm , with

Fig. 8.3 Schematic representation of a DLP 3DP process



minimum feature sizes between 50 and 250 μm . Very smooth surface finish can be obtained. However, SLA 3DP parts are generally brittle and not adequate for functional prototypes. Moreover, support structures and post-processing are usually required. Finally, the printing process takes a long time (All3DP 2019).

3 Digital Light Processing (DLP)

In 1987, shortly after the advent of SLA technology, Texas Instruments were the first to introduce the DLP technology which represents the core of this DLP 3DP method (Zhang et al. 2020). DLP (Fig. 8.3) is quite comparable to SLA. The main difference is that SLA employs a laser beam to cure point by point the layer of the model, whereas DLP is able to cure the entire layer at once resulting in faster build speeds. This is possible, thanks to digital micromirror devices (DMD). DMD are made by hundreds of thousand micromirrors contained in a matrix attached to a semiconductor chip. The micromirrors control the orientation of the light. Indeed, as light is reflected by them, they project the voxels of a 2D image towards the resin, hardening the exposed material. The light source of a DLP printer is usually a LED screen. The resolution of the 3DP part is dependent on the number of micromirrors in the DMD (Al Rashid et al. 2021). Digital micromirror devices (DMD) and focusing lens are contained into a digital light projector. Filters allow only light with requested wavelengths to arrive to the resin surface. The focusing lens focuses the light which is reflected off the DMD so that it precisely situates the layer onto the building platform at the right size/orientation (Cavallo 2022a).

How Does Digital Light Processing Work?

Similar to SLA, once the CAD design is uploaded to the printer software for slicing and printing activated, the printer's building platform is immersed in the resin vat. The digital light projector projects a layer of the digital model onto the resin. The light causes the resin to cure onto the building platform. Layers are built one on top of each other until each layer is completed. At the end of the printing process, the

part is then removed from the building platform for post-processing as in SLA (Chaudhary et al. 2022).

Advantages and Limitations

DLP printers can maintain relatively higher precision compared to other types of 3DP. 3D printing with DLP printers is generally more rapid than SLA, thanks to a full layer projection at once. Moreover, DLP 3DP parts are characterized by high isotropism (equality between X, Y, or Z planes). However, as for SLA, a post-processing of the 3DP parts needs to be performed (Zhang et al. 2020).

4 Liquid Crystal Display (LCD)

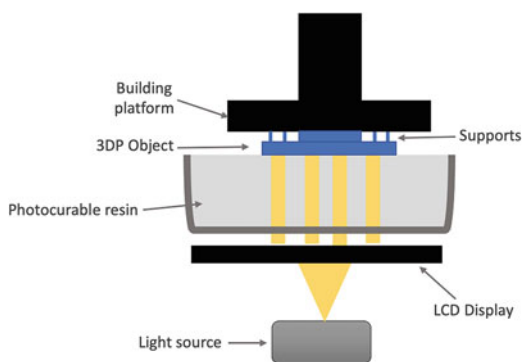
UV LCD 3DP (Fig. 8.4) was introduced as an affordable alternative to DLP and SLA. The main difference from them relies on the imaging system. Indeed, LCD 3DP uses an LCD display to selectively mask the light emitted by a LED lamp and projecting an image of an entire layer in the resin make it hardening. The lower part of the vat is made of a thin transparent film of ethylene propylene (FEP) or PolyTetraFluoroEthylene (PTFE), which let the light to be transmitted and prevents that the material sticks to the bottom of the vat (Mele and Campana 2022).

How Does Liquid Crystal Display Work?

The following are the steps that an LCD 3D printer employs to create a 3D object.

- Step 1: After the CAD is sent to the printer and printing starts, the building platform goes down to the resin tank, and the photopolymerizable liquid is then exposed to a light originating from a LEDs array and projected selectively from the LCD screen. The resin hit by the light changes to the solid state, whereas the part of the resin that is not needed will not be exposed to the light and keeps its liquid state.
- Step 2: The process is repeated until the entire object takes shape. Every time a layer is completed, the model is risen by the high of a layer to allow another layer to be added on top.

Fig. 8.4 Schematic representation of a UV LCD 3DP process



Step 3: Once the printing is finished, the object is raised out of the building platform, with the excess resin flowing back into the tank for further use. The final product is then post-processed by removing the support structures, smoothing surfaces, or further cured (Mele and Campana 2022).

Advantages and Limitations

LCD 3DP is a cost-effective VP technology and is characterized by a good resolution. Despite that, the LCD screen has a short life and needs to be substituted regularly. Moreover, when printing, partial light leakage could occur making this technology less precise than DLP (Quan et al. 2020).

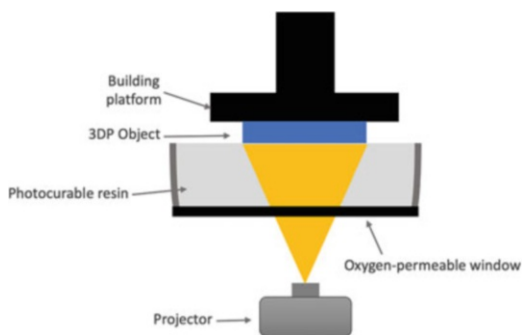
5 Continuous Liquid Interface Production (CLIP)

A further step forward in VP 3DP has been done in 2015 when continuous liquid interface production (CLIP) was first commercialized by Carbon 3D Corp. (Quan et al. 2020). CLIP (Fig. 8.5) uses an oxygen-permeable window instead of a normal glass window. The oxygen-permeable window creates a dead zone that lets the liquid resin flow in the space left between the 3DP object and the window (Pagac et al. 2021). In this interface, photopolymerization is inhibited by the oxygen by quenching the photoinitiator in the excited state or forming a peroxide (Bagheri and Jin 2019).

How Does Continuous Light Interface Production Work?

In CLIP, a digital light processing imaging unit projects continuously UV images of the CAD model through the oxygen permeable window, reaching the photopolymerizable resin. The resin hardens above the dead zone. As the 3DP process proceeds, the cured part is pulled out of the resin bath, and the liquid resin flows below it, maintaining a continuous liquid interface. When the object is completed, post-processing is performed (Düzgün and Nadolny 2018).

Fig. 8.5 Schematic representation of a CLIP 3DP process



Advantages and Limitations

One of the main advantages of continuous liquid interface production is that it permits the production of layer less parts. Indeed, final objects will not present the typical staircase effects of the other 3DP technologies. Moreover, CLIP prints with a very high speed reaching hundreds of millimetres per hour. Indeed, curing, resin renewal, and building platform movements are simultaneous (Düzgün and Nadolny 2018). Despite that, CLIP 3DP and its photocurable resins are very expensive. Moreover, since it's a newborn technology, there are not a lot of CLIP 3DP types available in the market (Cavallo 2022b).

6 Two-Photon Polymerization (TPP)

Two-photon polymerization (TPP) was first developed in 1997. In this 3DP technique, a near-infrared femtosecond laser determines the polymerization or crosslinking of the photopolymerizable resin (Jing et al. 2022).

How Does Two-Photon Polymerization Work?

During TPP three-dimensional printing, a femtosecond laser beams the photopolymerizable resin contained into the resin vat. One molecule of the photoinitiator absorbs two photon and pass from the ground state to the excited state starting a polymerization localized in the only region the laser is focused (Jing et al. 2022). Once the 3DP process is finished, the printed parts are placed in a suitable solvent to remove the uncured liquid resin and post-processed (Pagac et al. 2021).

Advantages and Limitations

One of the key advantages of TPP is that it allows the polymerization of the model directly in the resin tank. Differently to the other AM technologies, it eliminates the need for material deposition in a layer-by-layer (LbL) manner. Moreover, it has a high level of fabrication resolution. Indeed, objects characterized by structures with dimensions below 100 nm have been fabricated. However, that advantages come at the expense of long fabrication times (Nguyen and Narayan 2017).

7 Applications of Vat Photopolymerization 3DP in Drug Delivery

The application of VP in the field of drug delivery is very recent, and it is mostly explored for the development of oral dosage forms. Extensive research has been done to manufacture oral dosage forms which enable tailored release profiles satisfying patients' needs. In addition, there are research exploring the potentials of VP for the manufacturing of other DDSs, such as microneedles, and drug-eluting implants for ear diseases, among other applications.

Oral Dosage Forms

VP 3DP oral dosage forms comprise immediate release tablets, modified release tablets, tablets containing multiple active pharmaceutical ingredients (API) and capsules. Immediate-release tablets are oral dosage forms, which quickly disintegrate releasing the encapsulated drug. Differently modified release tablets are specially designed to obtain a certain drug release rate, timing and/or site (Pitzanti et al. 2021). Among the VP 3DP techniques, DLP and SLA were the most used for the development of oral dosage forms.

DLP was used by Krkobabić et al. to produce atomoxetine hydrochloride (ATH) tablets. DLP 3DP allowed the production of tablets with range of doses from 12.21 to 40.07 mg. Tablets with a higher drug content had shown an increased drug release rate after 8 h, with increasing mechanical properties, mass and dimensions (Krkobabić et al. 2020). Kadry et al. used the same 3DP technology to fabricate modified release tablets loaded with theophylline. Tablets with and without perforation were produced. 1% of drug loading was successfully achieved. The amount of drug released showed an increase with the increase in the number of perforations in the tablets (Kadry et al. 2019). Wang et al. fabricated torus shape modified release tablets loaded with 4-aminosalicylic acid (4-ASA) and paracetamol (acetaminophen) via stereolithography. The authors figured out that the drug dissolution profile was dependent on the % of cross-linkable polymer in the formulation but independent of the dissolution media pH (Wang et al. 2016). Robles Martinez et al. discovered that in SLA 3DP of tablets with different geometries (e.g. cube, disc, pyramid, sphere and torus) by changing surface area/volume ratio, a great difference on the drug release kinetics can be obtained (Martinez et al. 2018). Similar results were obtained by Karakurt et al., who manufactured with the same 3DP technology ascorbic acid tablets of different geometries (e.g. small and large tablet, coaxial annulus, 4-circle pattern and honeycomb pattern) with different surface area to volume ratios (Karakurt et al. 2020). Madžarević et al. explored the potential of LCD 3DP for the manufacturing of ibuprofen extended-release tablets. Printing wavelength showed to influence the printing time, the accuracy to the CAD model and drug release. Exposure time influenced the drug release formulation with high water content (Madžarević and Ibrić 2021).

VP was also used to manufacture multi-API tablets (polypills). For instance, Robles-Martinez et al. developed multi-layer tablets containing six drugs (e.g. paracetamol, caffeine, naproxen, chloramphenicol, prednisolone and aspirin) with SLA 3DP. The polypills were successfully printed via SLA and demonstrated excellent mechanical properties and different release patterns for all the six incorporated drugs (Robles-Martinez et al. 2019). A year later in the same research group, Xu et al. developed with SLA polyprintlets loaded with four antihypertensive drugs including irbesartan, atenolol, hydrochlorothiazide and amlodipine. In this study was discovered that one of the drugs (amlodipine) reacts with photocrosslinkable monomers (PEGDA) evidencing the importance of a pre-formulation study to figure out any possible interaction between the API and the resin matrix (Xu et al. 2020).

DLP 3DP was used by Chen et al. to fabricate mini-capsule devices containing islets. These devices were able to deliver satisfactory islet cell mass, avoid islet cells leakage and maintain long-term cell survival while allowing easy retrieval (Chen et al. 2022).

Transdermal Drug Delivery Systems

The second most investigated drug delivery field application of VP is transdermal drug delivery (TDD), in particular for the manufacturing of microneedles (MNs). MNs are tiny-sized needles, with height ranging from a few μm to up to 2 mm, which have the ability to go over the stratum corneum, outer skin layer, without arriving to the nerve endings located in the dermal tissues, guaranteeing painless drug administration (Mathew et al. 2021). The first paper about VP 3DP of microneedles is dated in 2018 when Pere et al. used SLA to manufacturing arrays containing pyramid or cone MN that were subsequently coated with insulin formulations by inkjet printing (Pere et al. 2018). Yadav et al. produced hollow MNs array conjoined with a reservoir with SLA 3DP. MNs were mechanically robust, possess a good penetration through porcine skin tissue and were able to deliver efficiently the antibiotic drug rifampicin (Yadav et al. 2021).

Mathew et al. compared three VP technologies (e.g. SLA, DLP and LCD) in the manufacturing of arrays containing conical and pyramidal hollow MNs. DLP was the 3DP technology able to manufacture MNs with needle height and tip size which had the optimal geometry. DLP printed MNs showed good mechanical strength and resistance to compression (Mathew et al. 2021). TPP was used by Cordeiro et al. to develop MN array templates with MNs of different shapes, height and interspacing (Cordeiro et al. 2020).

Scaffolds and Medical Devices

Recently, VP has been employed for the development of hearing aids with antibiotics. Vivero-Lopez et al. used DLP 3DP to manufacture hearing aids loaded with two antibiotics, ciprofloxacin and fluocinolone acetonide, for the treatment of ear infection. The devices guaranteed a prolonged release of the antibiotics over 7 days. Moreover, the systems avoid *P. aeruginosa* and *S. aureus* biofilm formation (Vivero-Lopez et al. 2021). More recently, Triacca et al. used SLA 3DP to produce levofloxacin-loaded ear implants with different designs. The implants possess good mechanical properties and guaranteed a 50% drug diffusion in over 3 weeks. They showed higher antimicrobial activity on *E. coli* than on *S. aureus* (Triacca et al. 2022).

A bladder device was manufactured by Xu et al. by SLA. The aim of the work was the achievement of extended and localized delivery of lidocaine hydrochloride. The 3DP device showed good mechanical properties and allowed a complete release of lidocaine within 4 days from the hollow devices whereas for up to 14 days the solid devices (Xu et al. 2021). Januszewicz et al. fabricated via CLIP technology intravaginal rings (IVRs) with geometric complexity within the cross-section. Several internal architectures were investigated with different unit cell designs (e.g. nodal, cylinder and honeycomb), size and thickness. They figured out that

this fabrication method enables to fabricate IVRs with compressive properties independent of the internal architecture (Januszewicz et al. 2021). Asikainen et al. used SLA to manufacture polycaprolactone scaffolds containing the model drug lidocaine. Compared to solid scaffolds, porous scaffolds determined a faster release of the model drug. The degree of porosity and surface to mass ratio did not show to have an effect to the release profile (Asikainen et al. 2018). Do et al. fabricated poly (ethylene glycol) dimethacrylate devices using a two-photon polymerization (TPP). Rhodamine B was used as a model drug. Hatching distance, slicing distance and pore size of the device showed to affect drug release profile. Moreover, the TPP 3DP devices were not cytotoxic on human embryonic kidney cells (HEK293), bone marrow stromal stem cells (BMSCs) or iPSCs (Do et al. 2018).

8 Conclusions

Over the last decades, there has been a growing interest in research on 3DP for drug delivery applications. Among all the 3DP technologies and compared to the conventional manufacturing method applied in drug delivery, VP can offer a better resolution of the 3DP parts, a faster fabrication, and allows the manufacturing of drug delivery devices with better functionality. Moreover, modifying the sizes, geometries and internal features of the 3DP part, it is possible to control the drug release profile and dosing. VP allows the manufacturing of patient-tailored systems improving medication adherence and the efficacy of treatment. Extensive research has been done, evident from the numerous research papers where the different VP technologies have been used for the manufacturing of oral dosage forms, microneedles, drug-eluting implants and medical devices.

Despite all these advantages, large-scale production of DDSs via VP is still far to happen. Indeed, the availability of photocurable biomaterials is still limited. Therefore, more research in this field needs to be carried out. Moreover, the commercially available VP 3D printers do not fulfil the good manufacturing practice (GMP) requirements, specifications indicated by medical agencies to guarantee the quality of the final product. Finally, regulatory challenges need to be addressed. Only after breaking these challenges, VP can be fully applied in the healthcare sector.

Multiple-Choice Questions to Check Knowledge in the Subject

1. Which of the following 3DP technologies doesn't belong to the vat-photopolymerization family?

- ☐ Digital light processing
- ☐ Liquid crystal display
- ☐ Fused deposition modelling

2. Which of the following part represents the core of a digital light processing 3DP?
- ☐ Liquid crystal display
 - ☐ LED screen
 - ☐ Digital micromirror device
3. What is the “dead zone” in CLIP 3DP?
- ☐ A zone where the liquid resin flow in the space left between the 3DP object and the window
 - ☐ A zone where photopolymerization is inhibited
 - ☐ All of the above
4. What is a photoinitiator?
- ☐ A molecule that creates reactive species when exposed to radiation
 - ☐ A molecule which when activated by the radiation catalyses the chain formation between monomers and oligomers
 - ☐ All of the above
5. What is the most studied application of VP in drug delivery?
- ☐ Transdermal drug delivery
 - ☐ Oral drug delivery
 - ☐ Ocular drug delivery
6. What are polypills?
- ☐ A group of tablets
 - ☐ Tablets containing more than one API
 - ☐ Tablets made by multiple sections
7. Which of the following are components of liquid light curable resins?
- ☐ Photoinitiator
 - ☐ Monomer
 - ☐ All of the above
8. What is the meaning of the abbreviation LCD?
- ☐ Liquid cationic display
 - ☐ Laser combined detector
 - ☐ Liquid crystal display

9. What is the light source of SLA 3D printing?

- ☐ An LCD screen
- ☐ A digital light projector
- ☐ A UV laser beam

10. Which of the following statements about microneedles is true?

- ☐ Are painful
- ☐ Have height ranging from a few microns to up to 2 mm
- ☐ Are able to reach the nerve endings

Answers

1. Fused deposition modelling
2. Digital micromirror device
3. All of the above
4. All of the above
5. Oral drug delivery
6. Tablets containing more than one API
7. All of the above
8. Liquid crystal display
9. A UV laser beam
10. Have height ranging from a few microns to up to 2 mm

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Chapter 9

Extrusion-Based 3D Printing Methods for Oral Solid Dosage Forms



Marilena Vlachou, Angeliki Siamidi, and Chrystalla Protopapa

Abstract The 3D printing (3DP) technology is predicted to be one of the main technologies for personalizing medicine delivery. Drugs with complex geometries and fillings can be synthesised using this approach to achieve the requisite release profile. Extrusion-based 3DP is the most investigated approach for assessing the potential of the technology to construct oral solid dosage forms with complicated features aiming at overcoming the typical production regime of ‘one size fits all’. The fused deposition modelling (FDM), the direct powder extrusion (DPE) and the semi-solid extrusion (SSE) are the three methods utilised in 3DP extrusion. The extrusion principles behind these techniques and their prospect for manufacturing oral solid dosage forms are presented in this chapter. Moreover, the advantages and limitations observed in the application of FDM, DPE and SSE for the production of these oral systems are also discussed. Further research is needed to apply this technology in health care for more efficient and personalised drug treatments.

Keywords Additive manufacturing · Extrusion-based 3D printing methods · Fused deposition modelling · Direct powder extrusion · Semi-solid extrusion · Tablets · Oral solid dosage forms

1 Introduction

The globe right now is going through the fourth industrial revolution, where technologies that seemed a fantasy are becoming a reality. As the manufacturing is digitalised and the 3D printing is finding more and more applications, the pharmaceutical industry couldn’t stand back. The conventional methods that are used for the preparation of tablets and capsules are time consuming, labour intensive and dose inflexible in contrast with the 3D printed tablets, which can have a wide range of

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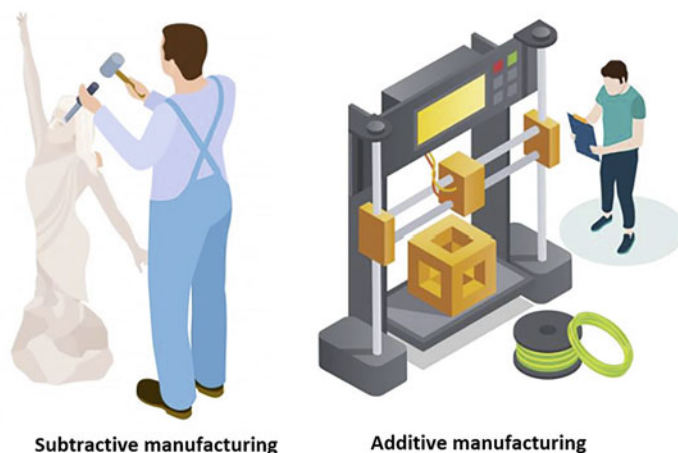


Fig. 9.1 Comparison of subtractive and additive manufacturing

dosage forms, designs and geometries. 3D printing is called additive manufacturing because it starts with nearly nothing, and the printer deposits material layer by layer to create an object into three dimensions, conversely to the classical way of making objects, where some material is removed to create the object (Fig. 9.1) (Durga Prasad Reddy and Sharma 2020; Lazaridou et al. 2022). There are different types of 3D printers, but they all have some common characteristics: the object to be printed has to be designed first on a software, splitting the object into horizontal layers. These data are then sent to the printer to start building layer by layer (CAD software) (Prasad and Smyth 2016; Lamprou et al. 2022).

In this chapter, the extrusion-based 3D printing methods for oral dosage forms (Fig. 9.2) (Goyanes et al. 2019a; Dumpa et al. 2021; Tagami et al. 2021) will be discussed. There are three techniques associated with extrusion-based three-dimensional printing (3DP): the fused deposition modelling (FDM), the direct powder extrusion (DPE) and the semi-solid extrusion (SSE). In FDM-based 3DP, thermo-plastic filaments are melted under high temperature and extruded through a nozzle to form a layer-by-layer 3D structure. In SSE-based 3DP, a continuous stream of semi-solid materials is extruded through a nozzle using compressed air or rotating screws to deposit the 3D structure. Flexibility and material availability have made the extrusion-based 3DP the most widely used technique for manufacturing pharmaceutical dosage forms. The principles of FDM-, DPE- and SSE-based 3DP techniques and contemporary research on fabricated innovative dosage forms are thoroughly discussed below.

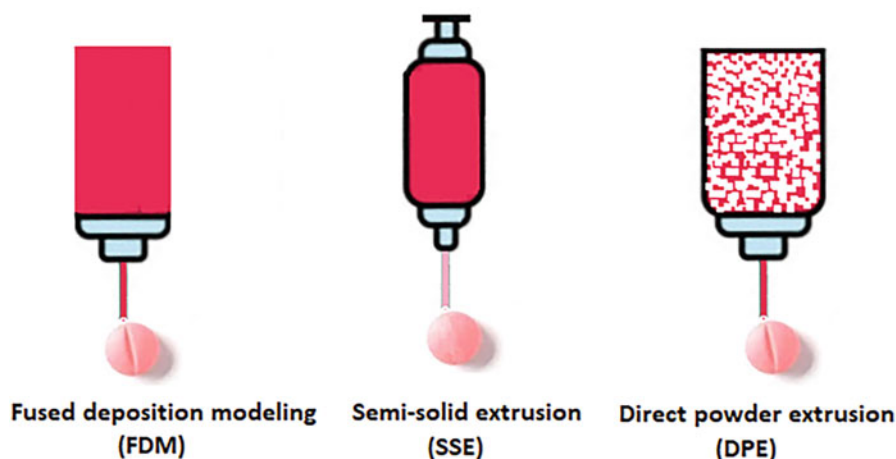


Fig. 9.2 Extrusion-based 3D printing methods

2 Fused Deposition Modelling

FDM, or fused filament fabrication, is an additive production method that fabricates 3D objects by extruding molten materials layer by layer on a platform. It is extensively used worldwide since 1988. This approach was mostly used for custom manufacturing, engineering, robotics, electronics and educational models, but advances in filament manufacturing and the diversity of accessible materials for printing have broadened its applicability to the medical/pharmaceutical area (Novakova-Marcincinova and Novak-Marcincin 2013).

The popularity of FDM is due to its usefulness, simplicity, variety of materials for various applications and moderately costly printers. The pharmaceutical industry is no exception; the FDM printing process is widely used to manufacture drug delivery systems (Mathew et al. 2020).

FDM printers are made up of two connected parts: the software and the hardware. The CAD software is used to create the 3D designs. The printing aspects (i.e. the temperature used to melt the filaments, the motions of the printer head) are controlled by the software (Skowrya et al. 2015). The filament extruders, the robotic section that directs the printer head's movement and the platform, are the most important pieces of hardware (Fig. 9.3). For the production of dosage forms, a suitable filament can be used (i.e. polylactic acid (PLA) and polyvinyl alcohol (PVA)) that is available from the market or can be generated by the hot melt extrusion technique (HME). Then, the active pharmaceutical ingredient (API) can be loaded onto the available filaments by filament impregnation into a saturated API solution. The API can be combined with polymers before the procedure if the filament is manufactured using the HME technique. Driving gears force the thermoplastic filament into the printer head to give a continuous feed of the filament. A heating part and a metal nozzle

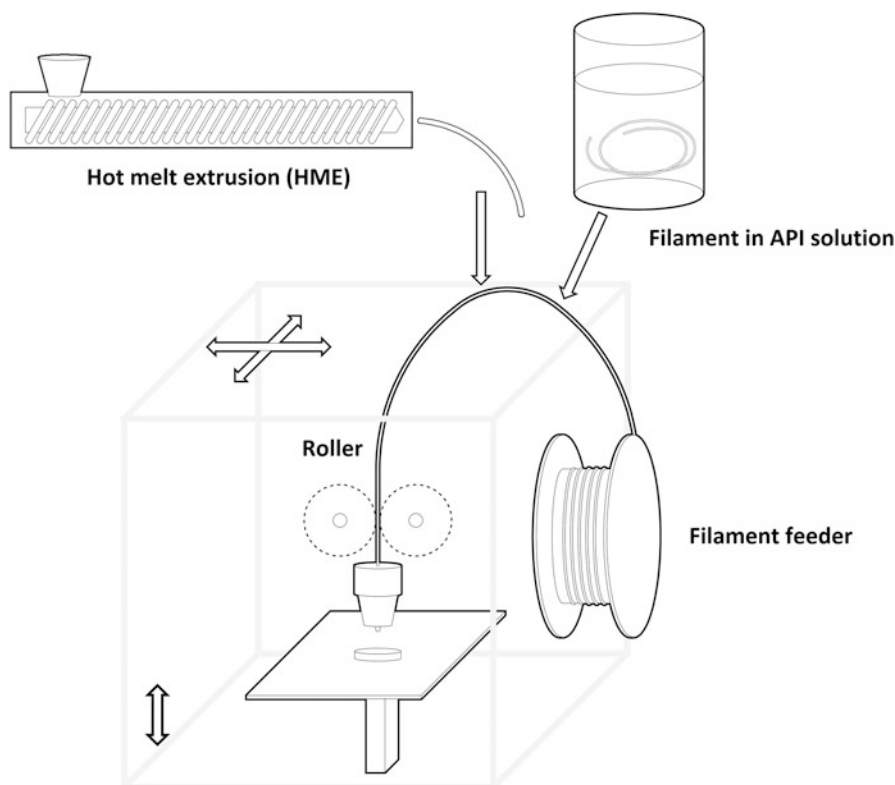


Fig. 9.3 Schematic representation of the fused deposition modelling technique (FDM)

make up the printer head. The heating part supplies the necessary temperature so that the filament would melt and be extruded via the nozzle. When the extruded materials cool down, they adhere on top of prior solid layer. A robotic section that travels in the various directions controls the printer head. The printing stage functions as a support stage for the printed product. After each layer of printing is done, the platform falls to allow the deposition of the following layer (Goyanes et al. [2015b](#)).

2.1 Advantages and Limitations of the FDM Technique as a 3DP Method for Oral Solid Dosage Forms

The extensive use of this technique, in fabricating pharmaceutical oral solid dosage forms, is due to the easiness of the printing process, its high-quality resolution, the availability and low cost of needed polymers with a variety of filaments and lower printer price. FDM has the benefit of quick solidification and requires no further drying/curing. Furthermore, the finished printed products have a great mechanical

strength. The printed layers' deposition is less complex since the melted components solidify at ambient temperature and aid in the transport of the next layer. Furthermore, the FDM printing technique offers a greater printing resolution than the SSE printing technology. Last but not least, this technique allows printing of hollow systems that can be filled with liquid, semi-solid or solid materials.

The main restriction of the FDM technology is the requirement for high temperatures to extrude the drug-loaded filaments, and therefore this method is not appropriate for thermo-labile APIs. Also, the drug loading to the filaments is limited. One more limitation is the step of HME, i.e. the preparation of the drug-loaded filaments. Another issue raised with this method is that the printed dosage forms' mechanical strength and restricted porosity may impede drug release via diffusion or erosion. Thus, for a fast drug release, the concept of printing tablets with perforating channels can be employed (Kempin et al. 2018; Kollamaram et al. 2018; Sadia et al. 2018a).

2.2 Recent Advances on 3D Printing Oral Solid Dosage Forms Fabricated by FDM

In this section, examples of novel dosage forms, such as immediate release, modified release and bilayer and gastric floating tablets, which have been attained by the FDM method, are being presented and summarised in Table 9.1.

2.2.1 Immediate Release Oral Solid Dosage Forms

After per os administration, immediate release formulations deliver a quick onset of action. The rapid tablet disintegration, followed by dissolution, renders the APIs immediately available to the blood circulation. The precise dosage required for the treatment of patients can be provided by 3DP technology, as the FDM-based 3DP technique is frequently utilised for the production of immediate release matrix tablets (Ashley 2015). To decrease the temperature needed for the filaments melting, during the 3DP process, researchers need to carefully choose the polymers to be used. In an experimental work, the scientists used Kollidon VA64, Kollidon 12PF and ramipril to produce filaments that successfully printed tablets at $\theta < 90\text{ }^{\circ}\text{C}$, a relatively low temperature (Kollamaram et al. 2018). Moreover, polyvinylpyrrolidone, Kollidon[®] VA64, polyethylene glycol 6000, polyethylene glycol 20,000 and poloxamer 407 were used in conjunction with the HME technique to fuse pantoprazole-loaded filaments. These filaments were then used to produce fast dissolving tablets (dissolution time $< 29\text{ min}$) at $\theta < 100\text{ }^{\circ}\text{C}$ (Kempin et al. 2018). For fast drug release without using disintegrants, channelled tablets have been fabricated with the FDM technique. The channels allow the gastrointestinal aqueous media into the tablet for a faster drug release. Indeed, tablets with various channel sizes and alignments were produced with hydrochlorothiazide, as a model drug, and tested. The drug release

Table 9.1 Examples of oral solid dosage forms produced by the FDM 3DP technique

Formulation	API(s)	Excipient(s)	Results	References
Immediate release tablets	Ramipril	Kollidon VA64, Kollidon 12PF	Successfully printed tablets at <90 °C	Kollamaram et al. (2018)
	Pantoprazole	Polyvinylpyrrolidone, Kollidon [®] VA64, polyethylene glycol 6000, polyethylene glycol 20,000 and poloxamer 407	Successfully printed tablets at <100 °C	Kempin et al. (2018)
	Hydrochlorothiazide		Successfully printed channelled tablets	Sadia et al. (2018a)
Oral fast dissolving films	Ibuprofen and paracetamol	Polyethylene oxide or PVA	Successfully printed oral films	Ehtezazi et al. (2018)
Modified release oral solid dosage forms	Paracetamol	Hypromellose acetate succinate	Successfully printed tablets	Goyanes et al. (2017)
	Budesonide	PVA	Successfully printed caplets	Goyanes et al. (2015b)
	5-fluorouracil	Sodium alginate, chitosan, PLA, Eudragit [®] L100–55 and Eudragit [®] S100	Successfully printed hollow tablets	Gioumouxzis et al. (2018)
Bilayer tablets	Deflazacort	Poly(e-caprolactone), Eudragit [®] RL100 and mannitol	Successfully printed hollow tablets filled with nano-suspension	Beck et al. (2017)
	Lamivudine	PVA, carboxymethylcellulose, PEG 400	Successfully printed hollow tablets	Smith et al. (2018)
	Rifampicin and isoniazid	PLA and PVA	Successfully printed hollow tablets filled with filaments	Genina et al. (2017)
	Enalapril maleate and hydrochlorothiazide	Eudragit EPO, triethyl citrate and tri-calcium phosphate	Successfully printed bilayered tablets	Sadia et al. (2018b)
	Paracetamol and caffeine	PVA	Successfully printed multilayered bilayered tablets	Goyanes et al. (2015c)
Gastric floating oral solid dosage forms	Domperidone	Hydroxypropyl cellulose	Successfully printed double-compartment tablets (one-compartment hollow)	Chai et al. (2017).

was found to be dependent on channels' size; shorter channels led to faster drug release than the longer channels (Sadia et al. 2018a). Apart from immediate release tablet formulations, fast dissolving per os administered films is an alternative system that offers rapid drug delivery (Pitzanti et al. 2021). Researchers have used the FDM technique to print single-layer and multilayered oral films. Filaments were produced by HME, using ibuprofen and paracetamol, as model drugs and either models, polyethylene oxide or PVA as polymers. The results indicated that the fast disintegration time is less than 50 sec for both films (Ehtezazi et al. 2018).

2.2.2 Modified Release Oral Solid Dosage Forms

Formulations defined, as modified release oral solid dosage forms, alter the drug release profile in order to change time course and/or location of drug delivery. This can help in better patient compliance, as fewer dosages are required, and more effective treatment can be achieved. The FDM-based technique uses a plethora of available polymers to print patient-tailored tablets of various geometries that modify drug release.

Scientists have used HME for the preparation of paracetamol filaments, using various grades of hypromellose acetate succinate. The produced filaments were then used to print tablets that released the API in a modified profile (Goyanes et al. 2017).

The same group of researchers has produced caplets (tablets in a shape of a capsule) based on the FDM printing. Using the HME method, PVA filaments loaded with budesonide were fabricated for the caplet production that was then enteric coated. The results indicated delayed drug release ($t > 2$ h) and sustained release thereafter (Goyanes et al. 2015b). The FDM technique has also been used for the nanosuspension conversion into a solid dosage form. Researchers produced different filaments with either poly(ϵ -caprolactone) or Eudragit[®] RL100 with or without mannitol. The prepared filaments were then soaked in deflazacort loaded nanosuspension and printed into tablets. The drug release studies indicated modified release dependent on the polymer used (Beck et al. 2017).

Another advantage of the FDM printing is that this technique enables the production of a capsule shell, where the API in either liquid or solid form can be hosted. For example, in a research work, 5-fluorouracil loaded alginate beads partially coated with chitosan were used to fill hollow printed tablets that were produced with Eudragit[®] L100–55 and S100 PLA filaments. The dissolution results indicated pH responsive drug release at pH 7.4 (Gioumouxouzis et al. 2018). In a different work, PVA filaments were used to print capsule shells with various wall thicknesses that resulted in delayed drug release formulations (Smith et al. 2018). In a more complicated approach, a 2-hollow compartments caplet was manufactured using PLA filaments. With the HME technique, rifampicin and isoniazid were compounded with polyethylene oxide to produce filaments that were inserted in the hollow compartments manually. One of the compartments was sealed with PVA. The results indicated modified and delayed drug release (Genina et al. 2017).

2.2.3 Bilayer Tablets

Another way to improve therapy is by increasing patient compliance by lowering the number of tablets required. The availability of tablets with combinations of APIs on the market has aided in increasing patient adherence to medication. However, even if this is a step closer to personalised medication, it cannot fully provide precise dosages and the drug release that the patients require (Mishra et al. 2014). The capability of FDM to produce drug devices with distinctive release profiles was explored in the following scientific works: researchers have used the FDM 3D printing to produce bilayer tablets containing enalapril maleate and hydrochlorothiazide. In each API (in different percentages), the required polymers and plasticizers were turned into filaments with HME. Then, the two produced filaments were fused through individual nozzles to produce the bilayered tablet that is closer to patient needs (Sadia et al. 2018b). In another work, scientists have used the same techniques to produce paracetamol and caffeine 3DP tablets. PVA was used as a polymer to produce the filaments with HME, while a dual FDM printer produced two designs: one including multilayers (each layer contained each API) and another one including a caplet set in within a larger caplet. Results from *in vitro* release studies indicated that the release profile depended on the device structure. More in detail, in the case of the multilayered design, the release of paracetamol and caffeine was simultaneous. In the case of the caplet embedded inside a larger caplet, the release of the drug from the internal caplet depended on the material used in the outer caplet (Goyanes et al. 2015c).

2.2.4 Gastric Floating Oral Solid Dosage Forms

In order to increase the drug retention time in the stomach, either for modified drug release or for topical treatment, light materials, that have sufficient buoyancy to float over the gastric content and remain for a longer time, are used for gastric floating drugs devices (Pawar et al. 2011). The ability of FDM to manufacture complicated structures (i.e. hollow tablets) offers a chance to fabricate gastro-floating drug devices. Researchers have used a commercially available PLA filament to produce a capsule shell that would host the riboflavin-compressed tablet in order to increase the retention time in the stomach by floating in the gastric content. The capsule shell was designed with two different compartments, one to host the tablet and one to be filled with air. The *in vitro* tests in HCl containing media revealed floatation, $t > 72$ h; *in vivo* studies on rabbits showed a $t > 72$ h gastroretention time, while dissolution results indicated 62% drug release at 72 h (Fu et al. 2018). In another work, scientists used domperidone, as a model drug, to produce gastric floating tablets with sustained release profile. The filaments were produced with HME using the API and hydroxypropyl cellulose. The printed tablet was in a hollow shape structure. *In vivo* results in rabbits indicated gastroretention for more than 8 h (Chai et al. 2017).

3 Direct Powder Extrusion

Currently, in the majority of the pharmaceutical publications associated with the fused deposition modelling 3D printing, an enormous part of the working time is spent on the choice of the excipients and in the optimisation to generate appropriate filaments for 3D printing. Moreover, most of the time, there are problems in the drug loading capacity of the selected polymers (Awad et al. 2018).

In 2019, another kind of material extrusion was introduced, the direct powder extrusion (DPE), where the powder is directly printed by using a tiny hot melt extruder within a print-head nozzle. Conversely to the FDM, the DPE is more accessible to the clinicians and researchers, as it bypasses the filament production step and shortens the timelines for drug development and optimisation (Seoane-Viaño et al. 2021c). Moreover, the DPE needs small amounts of excipients and drugs, making it the most appropriate technique for preclinical and clinical studies (Goyanes et al. 2019a; Fanous et al. 2020). A main limitation of the FDM 3D printing practice is the huge dependency on the mechanical and physical properties, the printing feasibility of the filament and the ambitious filament preparation, mainly when high drug loads are required (Goyanes et al. 2019a; Elbadawi et al. 2020; Melocchi et al. 2021). It is easy to observe that, as this technology does not need the filament preparation, using hot-melt extrusion (HME), lots of formulations that may not be possible to be printed with FDM, because the ingredients are thermosensitive or the characteristics of the filament are too flexible or too brittle, now they can be printed. As a result, the technical (physical and mechanical) limitations of the FDM and the difficulty of filament preparation, especially when high drug concentration is required, are overridden (Goyanes et al. 2019a; Elbadawi et al. 2020; Melocchi et al. 2021).

Goyanes et al. introduced in 2019, for the first time, the direct powder extrusion, a novel single step printing process for the development of printlets. Precisely, it is used for the preparation of a single-step solid amorphous dispersions itraconazole 35 wt% tablets, using various grades of hydroxypropylcellulose (HPC – UL, SSL, SL and L). As a result, all the printlets presented satisfactory physical and mechanical properties with not any drug degradation. The printlets also exhibited sustained release characteristics and high solubility. Consequently, this work confirmed the possibility of this innovative technology to conquer the main disadvantages of FDM 3D printing, which refer to the need to prepare the filaments by HME (Goyanes et al. 2019a).

Fanous et al. applied the direct powder extrusion method for the preparation of tablets having as active ingredient caffeine. The powder mixture was loaded, inserted into a cartridge-like head and printed with honeycomb design following heating of the extrusion cartridge. The mechanism of extrusion is the following: caffeine is dissolved in the excipient, hydroxypropylcellulose (HPC), as it melts at a lower temperature than caffeine, and the drug dissolves in the molten polymer (Abu-diak et al. 2011). In contrast to Goyanes, who used open hopper to load the powder material, they used prefilled cartridges avoiding the putative operator exposure (Goyanes et al. 2019a; Fanous et al. 2020).

4 Semi-Solid Extrusion

Semi-solid extrusion printing (SSE) is an additive manufacturing model, established in creating a solid object by depositing gels or pastes in successive layers. Semi-solid extrusion is under the category of ‘material extrusion’, which started with the development of FDM (Fang et al. 2021). Nonetheless, its printed material is semi-solid at room temperature, and the characteristics of the feedstock permit SSE to print at low temperature quickly, conversely to the other extrusion-based technologies. Consequently, SSE developed extensively in the bioprinting field, where it can print living cells capable to build sizable structures, like aortic valves (Firth and Basit 2018).

Prima facie, the SSE printing process has a lot of similarities with the FDM, the significant condition of an SSE printer being the extrusion process. In contrast to the other 3D printers, a syringe is filled with the gel and heated in the printer to transform into liquid (Fig. 9.4). Nonetheless, care has to be taken when heating, as the material can become much liquefied to hold any structure upon deposition. So, different experiments have to be done to find the appropriate temperature to print, using various materials (Solutions 2016). The material extrusion can be done using three methods: (1) solenoid-, (2) pneumatic-, and (3) mechanical-based system.

1. *Solenoid-based system*: It implements electrical vibes to a valve, which is placed at the base of the syringe. As a result, the vibes abolish the magnetic attraction arising between a floating ferromagnetic plunger and a ferromagnetic ring. As a result, the printer releases sub- μL volumes of material. However, this type of printers is not used in pharmaceuticals because of the viscosity of the gels/pastes applied. This mechanism is mainly used in bioprinting, as is frequently limited in

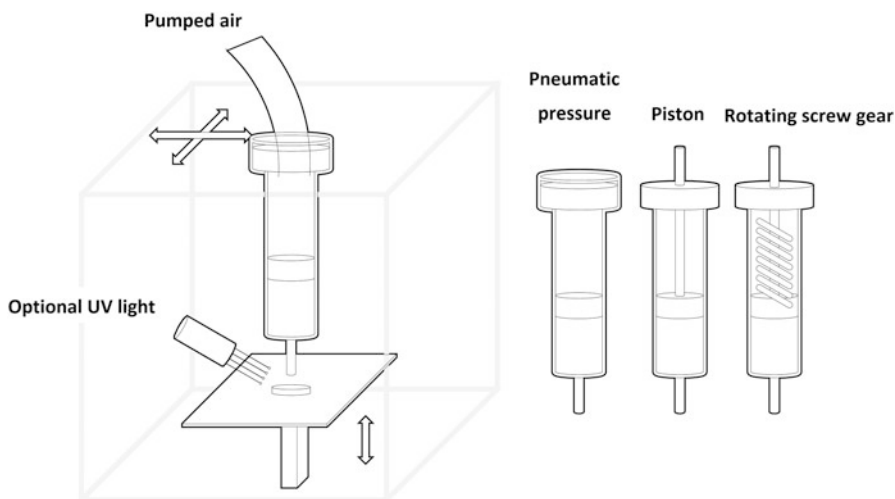


Fig. 9.4 Schematic representation of the semi-solid extrusion technique (SSE)

terms of its reproducibility. Also, some printers have a gap between the time of actuation and the valve opening, which can influence the consistency of the volume extruded, ending in an uneven deposition of the material (Firth and Basit 2018).

2. *Pneumatic-based system*: It implements air pressure to depress the syringe, which then extrudes the product. A valve on the nozzle ensures that the material will not be released when there is no pressure. Nonetheless, the gels that are used in pharmaceuticals are usually having high viscosity, so they can rely on a valve-free model. These systems, because they use compressed gas, are associated with a delay between initiating, dispensing and extrusion. As a result, it is difficult to assure the accuracy of material dispensed when using small volumes. This method is excellent when it is implemented with high viscous materials, because it is capable to reach compelling pressures without any effect on the integrity of the extrusion system (Firth and Basit 2018).
3. *Mechanical-based system*: Direct mechanical force is applied to the syringe. They can take either a screw-based configuration or a piston to monitor the extrusion of the gel, offering a much simpler mechanism than the pneumatic process. There is no need of a cumbersome compressed gas apparatus, thus improving the portability of the system. Furthermore, there is a better control of the extrusion flow, as the screw-based method can have pressure changes. Moreover, it is capable to print semi-solids of a higher viscosity than with a piston, as it has a screw-based mechanism which offers an increased level of spatial control (Firth and Basit 2018).

When the printing starts, the nozzle on the base of the syringe extrudes the semi-solid material. At this step, the viscosity of the material plays an important role. On the one hand, if the material is too viscous, it can block the nozzle and possibly damage the extrusion mechanism. Conversely, if it is too liquefied, the structure may not be able to hold on the requisite shape (Solutions 2016). To control the viscosity in an effective way, the formulation of the material can be adjusted to modify its physical characteristics in order to rise the liquidity. Otherwise, it is feasible to scale down the viscosity of the material by heating the syringe or by using a larger nozzle head, which is harder to clogging.

The position of the extrusion head is very important for the printing. Nevertheless, it is also of great importance to control the space from the bedplate to the viscosity of the material printed. If the distance is too big, the viscous solution will accumulate and solidify at the tip of the nozzle, whereas if it is too close, continuous extrusion would not be possible to be achieved, as it will be broken by the nozzle against the bedplate ending to an incomplete deposition.

A computer-controlled motor system is responsible for the position of the nozzle, giving the opportunity to the head to move along the x, y and z axes (Firth and Basit 2018). The bed is also very important in the entire process, not only for the material to adhere to the bed but also to be able to easily remove when the process is completed. To promote this, the print bed can be heated to minimise the stress in the base layers, which can end to immature release of the printed part. Yet again, the

temperature has to be carefully controlled to assure that the material is capable to solidify adequately, resulting to the retune of its shape.

4.1 Pharmaceutical Applications of the Semi-solid Extrusion

The application of SSE is relatively a novel approach in pharmaceutical formulation, offering the ability to create complicated dosage forms, avoiding the harsh conditions that are associated with the other 3D printing techniques, like the FDM (Goyanes et al. 2015a). The nature of the materials that are used allows the extrusion process to be performed at low temperature without compromising the accuracy (Aita et al. 2020). Initially, SSE was used to prepare polypills and tablets but now is also used for the preparation of chewable tablets (Goyanes et al. 2019b), immediate and controlled release dosage forms, orodispersible films (Elbl et al. 2020), implantable patches (Yi et al. 2016) and rectal suppositories (Seoane-Viaño et al. 2021b). The most common route for drug administration is the oral, as more than 60% of the drugs today are administered orally (Awad et al. 2020). This is because it is convenient, cost-effective and easy to administer (Homayun et al. 2019).

4.1.1 Polypills

Polypills incorporate various active ingredients in one single dosage form (Pereira et al. 2019). SSE has been used for the production of polypills aiming at achieving different release profiles for each drug (Fig. 9.5). Figure 9.3 demonstrates the production of a polypill by combining nifedipine, captopril and glipizide (Khaled et al. 2015a). This combination of the drugs, in one tablet, will be very beneficial for the treatment of diabetes. To do so, each drug has to be released independently. As a result, captopril is enclosed in a compartment encapsulated by a porous cellulose acetate shell to limit the release of the drug with osmosis, ensuing zero-order release kinetics. On the other hand, both glipizide and nifedipine were enclosed in two separate compartments, which were encapsulated in the porous shell all over the surface, except the superior face, to permit release of the drug by diffusion, ending in a first-order release profile (Seoane-Viaño et al. 2021a). Furthermore, an HPMC hydrophilic matrix was used to cut down the release of the drug for both glipizide and nifedipine.

Another two attempts, from a RegenHu 3D Discovery printer and Cadila Pharmaceuticals Ltd., were made to create a polypill with five active ingredients. The RegenHu 3D Discovery printer extruded, with one print, five different active ingredients making a tablet that contains all of them. Cadila Pharmaceuticals produced, for the first time, the only commercially available polypill, named Polycap, which is used for cardiovascular diseases and contains atenolol, pravastatin, aspirin, ramipril and hydrochlorothiazide in five separate rooms each with different release profiles. The active ingredients ramipril, pravastatin and atenolol were mixed with

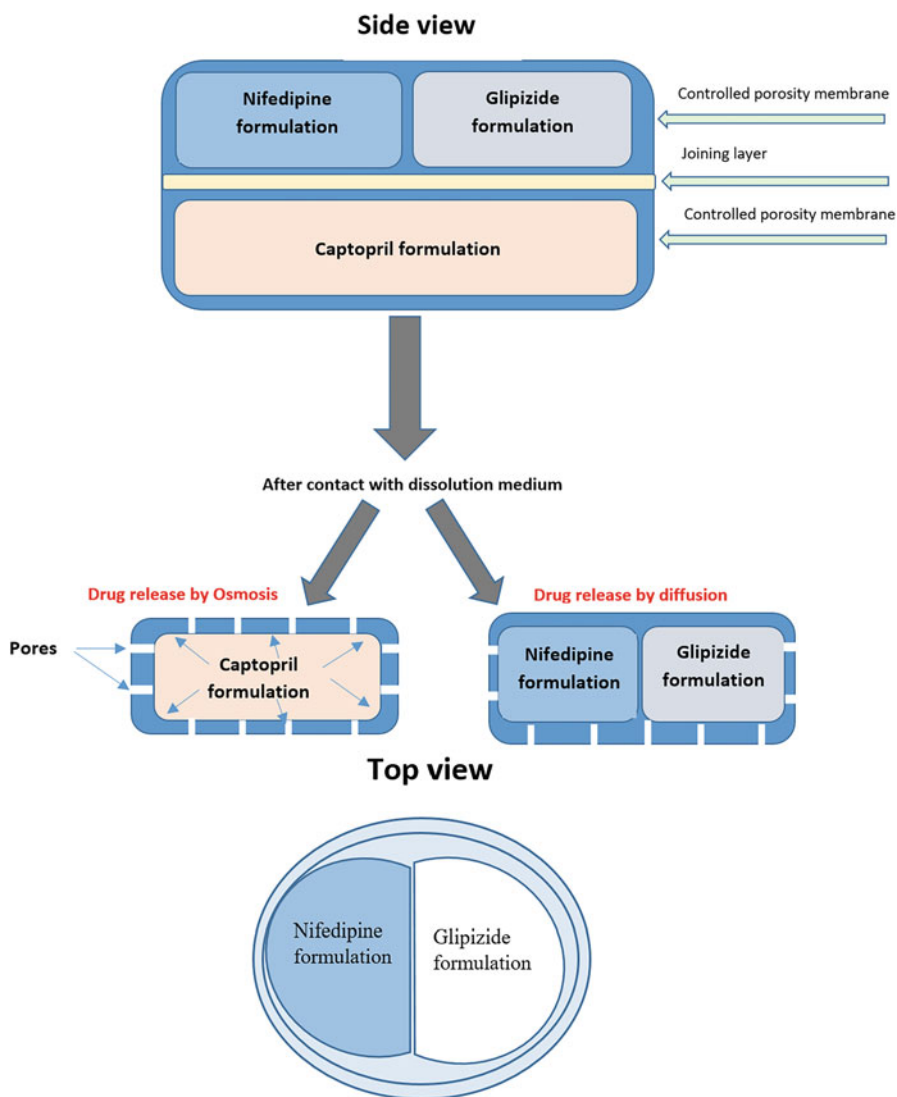


Fig. 9.5 A polypill consists of three different drugs, separated into different rooms with various release mechanisms

HPMC, a hydrophilic matrix, whereas hydrochlorothiazide and aspirin were mixed with a disintegrant and extruded on the top of the sustained release tablet, achieving immediate release (Khaled et al. 2015b).

4.1.2 Immediate Release Tablets

SSE 3DP is extensively used for tablet preparation. The produced printlets can be used when the patient wants to avoid swallowing the chewable printlets or when there is a need of high drug loadings adapted to the needs of the patient. The SSE 3DP can produce tablets with various release profiles, both immediate and controlled. The SSE 3DP proved that it can be used in the production of immediate release tablets. As the main benefit from using 3DP is the customisation of the dose for each patient, SSE was used to prepare immediate release tablets, having as active ingredient levetiracetam, which is used to treat epilepsy. The dose is increased to paediatric patients over the weeks so the flexibility offered by the SSE 3DP is essential (El Aita et al. 2019). To achieve the immediate release profile, the appropriate excipients need to be used. Cyclodextrin is well known for increasing drug solubility. As a result, it is used as a filler in the SSE 3DP extrusion to achieve the immediate release of carbamazepine printlets (Conceição et al. 2019). Except cyclodextrin, other excipients have been used in the preparation of immediate release tablets, like PEG 4000, which has low melting point and often used to prepare immediate release solid dispersions. PEG 4000 is not used for the preparation of tablets using direct powder compression, due to its adhesive behaviour, but is useful for 3DP dosage forms.

Also, it is possible to use SSE 3DP to prepare immediate release tablets with high drug loads. The following two examples are typical: initially, paracetamol tablets with drug loads up to 80% w/w were produced (Khaled et al. 2018). The tablets were capable of releasing up to 90% of the drug in 10 min. Next, tablets, which were loaded with 96% w/w levetiracetam, releasing 85% of the drug after 15 minutes, were prepared (Cui et al. 2020).

4.1.3 Controlled Release Tablets

The use of the SSE 3DP can achieve the production of controlled release matrices by developing two-layer tablets using various viscosity grades of HPMC. It was found that as the quantity of HPMC hydrogel is risen, a more delayed drug dissolution was observed, and the hardness and weight of the produced tablets are reduced (Cheng et al. 2020). Typical is the study that was done with the production of controlled release tablets of guaifenesin, using SSE 3DP, and compared them with the already commercially available tablets (Khaled et al. 2014). It was found that they had the same release profile, with an initial burst release and then a sustained release profile during 12 h.

To achieve different drug release profiles, thermosensitive gelatin pastes can also be used in combination with other excipients. For example, the release after the plugin of 30% w/w HPMC lasted for 24 h in comparison with the 4 h release observed after the addition of 15% w/w HPMC (Yang et al. 2020). Moreover, the release can be influenced by the internal structure of the tablet. When the grid width

risers, the drug release is higher, which can be explained by the higher surface area of the tablets that promote drug diffusion and dissolution (Cui et al. 2019). Finally, gastroretentive drug delivery systems can be used to delay the stomach residence time of drugs that are acting locally in the stomach or are soluble at acidic pH and are unstable in the alkaline environment (Li et al. 2018).

4.1.4 Chewable Printlets

Regardless of the advantages of solid dosage forms (e.g. capsules and tablets) and liquid dosage forms (e.g. suspensions and solutions), some limitations are still present (Wening and Breitzkreutz 2011; Sam et al. 2012). On the one hand, the main disadvantage of solid dosage forms is the swallowing issues by some patient populations, like paediatrics and geriatrics, and on the other hand, liquid dosage forms are having stability issues and dosing errors (Sam et al. 2012). However, chewable formulations, like gummies, chewable tablets, gums and lozenges, which are easy to administer, are safe, and they do not have any stability issues and are gaining attention (Fig. 9.6). SSE 3DP can be used to create sophisticated personalised chewable formulations with different size shapes and flavours (Trenfield et al. 2019; Seoane-Viaño et al. 2021c). Until today, the jelly-like formulations are gaining attention, to be 3D printed, as they have the ability to modify the formulation's rheological properties, like texture and viscosity (Saha and Bhattacharya 2010; Shahbazi and Jäger 2021).

Chewable formulations are not limited by the size, as they are developed to be chewed before swallowed. Also, because they disintegrate in the mouth, some of the drug is dissolved in the saliva and absorbed from the buccal cavity, avoiding the first-pass metabolism from the gastrointestinal tract, thus rising the drug's bioavailability. Additionally, they can be administered without the need for water, making

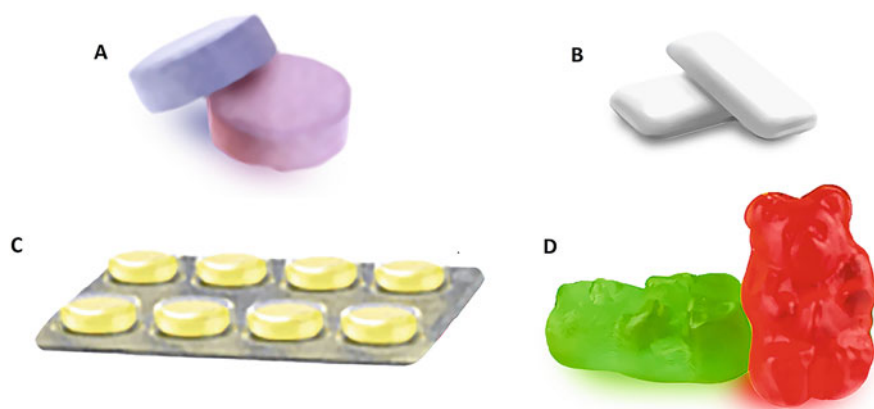


Fig. 9.6 Images of (a) chewable tablets, (b) chewing gums, (c) lozenges and (d) chewable gummies

them a convenient and easy way for drug administration. Last but not least, chewable formulations are suitable for patients that are having difficulties with swallowing, like paediatric and geriatric patients and those suffering from dysphagia, improving their compliance and acceptability of the treatment (Liu et al. 2014; Krekeler et al. 2020).

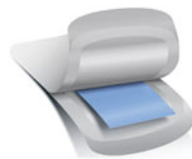
Regarding the disadvantages, sometimes it is hard to load chewable formulations with drugs that they have pungent and unpleasant taste (e.g. bitter) without adding a lot of flavouring agents and sweeteners. Also, incidents have been recorded, where patients damaged their tooth due to the excessive hardness of the tablet or faced an oesophageal irritation. Finally, chewable tablets are hygroscopic, so they have to be stored in a dry place in airtight containers (Rodríguez-Pombo et al. 2022).

Healthcare professionals have to pay attention to swallowing difficulties, as 1 in 11 patients is frequently facing difficulties in swallowing capsules and tablets (Schiele et al. 2013). In patients with dysphagia, chewable formulations can help them promote the passage into the gastrointestinal tract over the chewing process (Rodríguez-Pombo et al. 2022). Moreover, as people are getting older are finding the swallowing of tablets uncomfortable, compromising their treatment by dose variation or dose dumping. Taking this into consideration, chewable formulations are very suitable for the elderly (Breitkreutz and Boos 2007). Finally, children, besides having difficulties in swallowing tablets, are in demand for chewable formulations, and they need personalised doses to avoid lower dose or overdose. Characteristic is a clinical trial, which asked children between 4 and 11 years old to choose the form of their treatment and 79% of them asked for chewable tablets made with SSE 3DP, while at first, not knowing that the tablets could be chewed, they were pro the digital light processing method to make their tablets (Januskaite et al. 2020).

Because the existing production methods of chewable tablets, although they are cheaper, are inappropriate for personalisation, there is a need for new processes that can be both flexible and simple, allowing the on-demand preparation of medicines. As a result, the SSE 3DP can offer personalisation, by printing, based on patients' needs (Thabet et al. 2018; Khan et al. 2022; Zhu et al. 2022). Consequently, the patients can involve in the design process and modify the shape, flavour, colour and size of the chewable formulation, according to their preferences. It is found, from an acceptability study, that due to the ability to choose the characteristics of their medicines, through the software, the systematic intake of the tablets increases and consequently the effectiveness of their treatment (Duan et al. 2012; Ong et al. 2022).

An indicative example is the application of SSE 3DP in the preparation of chewable isoleucine tablets for children with the maple syrup urine disease, which is a rare metabolic disease, defined by the lack of the enzyme complex branched-chain *alpha*-keto acid dehydrogenase. The produced triplets were used in a clinical trial, which showed that the isoleucine blood levels were tighter controlled than with the commercially available tablets. Moreover, caregivers mentioned that the flavoured triplets were more acceptable from the children which is really important in this kind of diseases (Goyanes et al. 2019b).

Fig. 9.7 An example of orodispersible films



Other different approaches were the creation of paediatric-friendly SSE 3D printed oral dosage forms, based on chocolate and cereals using with active ingredients, the hydrophilic paracetamol and lipophilic ibuprofen. The release behaviour of each drug was based on its physicochemical characteristics (Karavasili et al. 2020).

4.1.5 Orodispersible Films

Another way to increase patient acceptability to populations that are suffering from swallowing difficulties are the orodispersible films (ODFs), notably because they are administered without water (Fig. 9.7). For example, the preparation of warfarin ODFs, using SSE 3DP, simultaneously satisfies the need to adjust the dose to the patient's needs and the difficulty in swallowing (Sjöholm and Sandler 2019). Without this approach, the patient needs to cut the tablets to achieve the required dose, compromising the correct administration of the dose. Another application of SSE, in preparing ODFs, was made in a drug used for allergic rhinitis, levocetirizine hydrochloride. The dose of this drug in children depends on the age and is usually administered as oral solution or fixed-dose tablets. By the use of ODFs, the dose can be tailored to each age group avoiding dose errors originating from the use of oral solutions (Yan et al. 2020). Finally, ODFs can be used, except from children and patients with dysphagia, to psychiatric patients that are non-adherent. ODFs are harder to get out of the mouth on purpose and do not cause choking after the administration (Cho et al. 2020).

4.2 *Regulatory of SSE Technique as a 3DP Method for Oral Solid Dosage Forms*

The pharmaceutical industry is greatly regulated, so 3 DP is facing various challenges for its extensive adoption in the healthcare system. Until today, the only FDA-approved and commercially available 3D printed medicine is the Spritam[®], from Aprelia Pharmaceuticals (Apricia 2015). However, the on-demand preparation of medicines with 3D printing still needs regulatory agreement. Also, another vital condition for the implementation of 3DP, in the healthcare system, is the standardisation of 3D printers to fulfil the regulatory and quality control conditions, and the use of an authorised software to supervise the whole system. Furthermore,

the process analytical technology can be used to assure better process performance and product quality (Akm Khairuzzaman 2018). Finally, it is worth mentioning that 3D printers were not developed for pharmaceutical production, and that is why they, at present, do not meet the good manufacturing process (GMP). Nonetheless, SSE 3DP has a high potential to be used in the production of medicines, as it uses excipients which are recognised as safe, like pharmaceutical and food-grade excipients (Elder et al. 2016).

4.3 Advantages and Disadvantages of the SSE Technique as a 3DP Method for Oral Solid Dosage Forms

The most significant advantage of chewable formulations is the ability to be administered to patients that have swallowing difficulties, like those suffering from dysphagia, geriatric and paediatric patients, achieving the increase of acceptability (Liu et al. 2014; Krekeler et al. 2020). Moreover, they can be administered without water making their use more convenient. In addition, because they are chewed, they disintegrate in the mouth, and some of the drug is dissolved in the saliva resulting to the absorption from the buccal cavity bypassing the first-pass effect and rising the bioavailability of the drug. Furthermore, as the tablets are chewed, their size is not limited to what can be swallowed by the patient. However, regarding the disadvantages, it can be hard to load chewable formulations with drugs that have unpleasant taste without adding a lot of flavouring agents or sweeteners (Rodríguez-Pombo et al. 2022). Also, as they are hygroscopic, have to be stored in a dry place in airtight package. Finally, the chewable formulations have been associated with tooth damage and denture breakage, as a result of excessive tablet hardness.

5 Conclusions and Future Perspectives

The 3DP technology has transformed the biocompatible materials field by delivering a low-cost, customised solution for medical applications, such as organ transplantation, tissue engineering and prosthetics. 3DP is projected to be a trend in the pharmaceutical industry for drug formulation, particularly personalised medications. The extrusion-based printing is the most often utilised 3DP technology researched for the fabrication of pharmaceutical dosage forms. When compared to other printing methods, the utilisation of this technique is rapidly increasing as the intricacy of the printing process, the fragility of the finished result and the scarcity of biomaterials have hampered the advancement of technologies, like stereolithography, inkjet printing and SLS. Some of the benefits of extrusion-based printing include the ease of application and the quantity of the biocompatible materials available for the creation of efficient dosage forms. The 3DP technology, based on SSE, has the

benefit of printing nearly anything that can pass through the micro-nozzle. However, when compared to the FDM, the difficulties in changing the needed viscosity and the additional process of drying have hampered its advancement. FDM's versatility and cost-effectiveness allow it to govern the production of medicinal dosage forms. Additional studies on the rheology of the materials used and the drying process might lead to more SSE applications in the future. On the other hand, SSE has the benefit of being able to employ readily accessible excipients that have been shown to improve the characteristics of pharmaceutical formulations. Furthermore, SSE has the benefit of materials extrusion without the use of high temperatures, which impacts the stability of the APIs.

3DP technology is projected to be adopted in the healthcare system, allowing healthcare providers to design patient-based medication devices. To guarantee the efficacy and safety of the produced drug containing device before dispensing, real-time drug content evaluation is necessary. This evaluation must be cost-effective, non-destructive and not to necessitate the presence of a highly qualified operator. Therefore, more advances of both the printing technique and post-printing medication assessment are necessary.

Multiple Choice Questions

(1) The direct powder extrusion:

- (a) Needs higher amount of excipients and drug
- (b) *Bypasses the filament production step*
- (c) Has huge dependency on the mechanical and physical properties
- (d) Cannot print thermosensitive drugs

(2) This system mainly used for bio printing:

- (a) *Solenoid-based system*
- (b) Pneumatic-based system
- (c) Mechanical-based system

(3) The position of the extrusion head is vital for printing with SSE:

- (a) *True*
- (b) *False*

(4) SSE 3DP can offer:

- (a) Personalisation/flexibility
- (b) The ability to prepare polypills
- (c) The ability to prepare orodispersible films
- (d) *All of the above.*

(5) FDM stands for fused deposition modelling.

- (a) *True*
- (b) *False*

(6) Which additive manufacturing method(s) use(s) powder as feedstock?

- (a) FDM
- (b) *DPE*
- (c) SSE

(7) Thermosensitive ingredients should better be printed with the technique of:

- (a) FDM
- (b) *DPE*
- (c) SSE

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Chapter 10

Binder Jetting 3D Printing in Pharmaceutical Manufacturing



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Abstract This chapter begins by introducing the concept and basic working principle of binder jetting (BJT) 3D printing. This is followed by discussing the material requirements for the ink and powder feedstocks in BJT for pharmaceutical manufacturing. Several process parameters and main considerations for jetting the ink, spreading the powder, and controlling the properties of the 3D printed dosage forms are highlighted and explained. Material formulations and properties of the 3D printed solid dosage forms reported in the literature are tabulated. At the end of this section, several key technical challenges that remain to be addressed are summarized.

Keywords Binder jetting · Inkjet printing · Material selection · Process optimization

1 Introduction to Binder Jetting (BJT)

According to ASTM F2792, binder jetting (BJT) is defined as “an additive manufacturing process in which a liquid bonding agent is selectively deposited to join powder materials.” BJT was first developed at MIT and licensed to several companies for various commercial applications, ranging from producing sand casting molds to ceramic or metal green parts (Gibson et al. 2021). In a typical BJT process, a thin layer of powder is first spread, followed by jetting a liquid ink that selectively binds the powder. The powder spreading and ink jetting process is repeated until the entire 3D object is printed. At the end of printing, the as-printed

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Table 10.1 List of powders (p), liquid binders (l), and active pharmaceutical ingredients (APIs) reported in the literature for binder jetting of fast disintegrating solid dosage forms

Powder (p)	Liquid binder (l)	API	References
Lactose monohydrate and Kollidon [®]	Kollidon [®] in water	Indomethacin (p)	Chang et al. (2021)
Ketoprofen, lactose monohydrate/microcrystalline cellulose/mannitol, polyvinyl pyrrolidone (PVP), and silica	Ethanol and polyethylene glycol (PEG) in water	Ketoprofen (p)	Kreft et al. (2022)
Microcrystalline cellulose and PVP	PVP, Tween [®] 20, and sodium dodecyl sulfate in water/ethanol in water/methanol/isopropanol/dichloromethane/acetonitrile	Quinapril hydrochloride (p)/clotrimazole (p)	Kozakiewicz-Latała et al. (2022)
Microcrystalline cellulose and Aerosil [®] 200	Isopropanol aqueous solution, PVP, and glycerin	Levetiracetam (p)	Wang et al. (2021)
Lactose and PVP	PVP in water	Paracetamol (p)	Wang et al. (2022)
VisiJet [®] PXL Core powder, lactose/lactose and calcium sulfate hemihydrate and sodium croscarmellose/calcium sulfate hemihydrate and sodium croscarmellose	Hydroxypropyl cellulose (HPC)/Kollidon [®] /PEG/hydroxypropyl methylcellulose	Indomethacin (p)	Chang et al. (2020)
Lactose and powdered sugar	PVP and Tween [®] 20	Acetaminophen (p)	Wilts et al. (2019)
Lactose, PVP, mannitol, and colloidal silicon dioxide	Ethanol, PVP, and methylene blue in water	Acetaminophen (p)	Yu et al. (2009a, b)

object embedded within the powder bed is allowed to rest and further consolidate before being removed from the powder bed. Any loose powder is cleaned off from the print object using a brush, compressed gas, or a sieve shaker. The printed object may be further dried or coated. For pharmaceutical applications, BJT has been successfully adapted for producing both fast disintegrating and sustained release solid dosage forms, as summarized in Tables 10.1 and 10.2, respectively. The method has been scaled up for commercial production of Spritam[®]—the first FDA-approved 3D printed orally disintegrating tablet for treating epilepsy. Several recent review papers already exist (Goole and Amighi 2016; Prasad and Smyth 2016; Norman et al. 2017; Sen et al. 2021a). This book chapter focuses on some of the main fundamental considerations for those who are interested in adopting this technology. We first lay out the material considerations in terms of the ink and powder requirements, options for inclusion of the active pharmaceutical ingredient (API), and binding mechanisms. Then, we discuss the process considerations, highlighting the key process parameters to consider and adjust for successful printing and control of the final properties. Remaining technical challenges are presented in the last section.

Table 10.2 List of powders (p), liquid binders (l), and active pharmaceutical ingredients (APIs) for binder jetting of sustained release solid dosage forms

Powder (p)	Liquid binder (l)	API	References
Calcium sulfate hemihydrate (CSH)	2-pyrrolidone	Hydroxychloroquine sulfate (l), favipiravir (l), and ritonavir (l)	Lu et al. (2022)
Microcrystalline cellulose/microcrystalline cellulose, lactose, and Eudragit® L100	Eudragit® E100/L100 in ethanol/acetone, Eudragit® RLPO in acetone/diclofenac, Kollidon® K-25 in methanol/water	Chlorpheniramine maleate (l)	Rowe et al. (2000)
Cellulose powder, lactose	Eudragit® E100 in ethanol/acetone, Kollidon® K25 and tween® 20 in water	Chlorpheniramine maleate (l)	Katstra et al. (2000)
Kollidon® SR and hydroxypropyl methyl cellulose (HPMC)	Triethyl citrate in ethanol	Pseudoephedrine hydrochloride (l)	Wang et al. (2006)
HPMC E50, PVP, and colloidal silicon dioxide	Ethyl cellulose (EC)/PVP/sodium lauryl sulfate/stearic acid (SA)/Eudragit® RS100 in ethanol	Acetaminophen (p)	Yu et al. (2007)
HPMC, EC, PVP, and colloidal silicon dioxide	EC in ethanol	Acetaminophen (p)	Yu et al. (2009a, b)
HPC, magnesium stearate colloidal silicon dioxide	Ethanol in water	Caffeine (p)	Infanger et al. (2019)
CSH, vinyl polymer, and carbohydrate	2-pyrrolidinone in water	5-fluorouracil (via a separate coating solution)	Shi et al. (2019)

2 Material Considerations

BJT complements other 3D printing methods, such as material extrusion (MEX) and powder bed fusion (PBF), which rely on heat to deposit material or consolidate the print structure (Goole and Amighi 2016). BJT supports room temperature operations, making it suitable for handling and processing heat-sensitive ingredients. Also, during the printing process, loose powders serve as a natural support, enabling the printing of more intricate and overhang structures (Gibson et al. 2021). The success of BJT is contingent on selecting the appropriate liquid ink and powder feedstocks. In BJT, each ingredient may be introduced in the liquid form through the inkjet print head or in the powder form onto the build bed. A basic formulation includes at least an excipient, an API, and a binder. Given the inkjet print head deposits the liquid in fine droplets, typically on the order of tens of pico-liters, and that the ingredient concentration is usually kept low to maintain a sufficiently low viscosity for jetting, the total amount of ingredient may be limited (Chang et al. 2020). Excipients that make up much of the dosage form are usually fed to the printer as powders. Binders may be incorporated in the liquid ink, powder, or both to

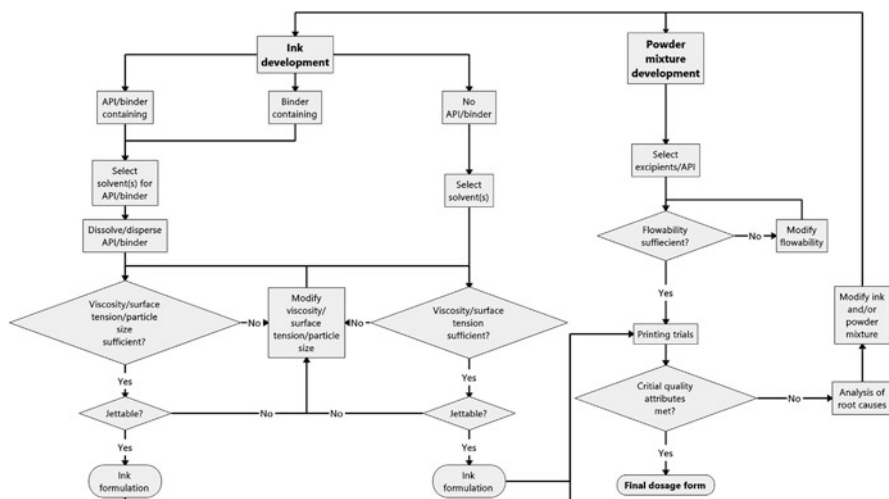


Fig. 10.1 Example BJT formulation development workflow. (Reproduced from Infanger et al. 2019)

increase the total concentration and maximize the binding effect (Chang et al. 2020, 2021). Likewise, the API may be dissolved or dispersed in the ink (Sen et al. 2020) or blend with the excipient powder using v-blending (Chang et al. 2020, 2021) or resonant acoustic mixing (Osorio et al. 2016). One key advantage of introducing the API via the print head is the ability to vary the local concentration in the solid dosage form to control the drug release profile (Rowe et al. 2000; Wang et al. 2006; Yu et al. 2007, 2009a, b). Other major factors to consider are how the inclusion of each ingredient modifies the ink jettability and powder flowability as discussed in the following sections. Figure 10.1 shows an example workflow for formulation development of BJT.

In terms of the liquid ink, the first and foremost is the chemical compatibility with the print head. This is especially important for inks involving an organic solvent. Solvents that are great for dissolving water-insoluble APIs and polymers may affect the print head drive electronics, contaminate the product, reduce the longevity of the print head, and lead to catastrophic failure of the print head. General information on chemical compatibility is usually available from the print head manufacturer and should be carefully evaluated before finalizing the ink formulation and/or print head selection. Some print head manufacturers may also offer a compatibility testing kit for custom ink formulations. Even for inks with carrier solvents that are chemically compatible with the print head, one should carefully evaluate how the ink formulation affects the longevity and reliability of the print head. Inks that contain particles may be jetted with appropriate conditions but may also increase the chance of nozzle clogging. Further, the inclusion of particles will also likely modify the jet breakup and drop formation process due to finite size of the particles and local particle density fluctuations (Ma et al. 2008; Furbank and Morris 2004; Wang et al. 2012). For inks containing polymers, the polymers may also cause fouling and performance issues,

Table 10.3 Reported fluid properties of liquid binders used for pharmaceutical BJT

Density (g/mL)	Viscosity (mPa s)	Surface tension (mN/m)	References
0.93–1.00	1.4–4.2	29.7–46.8	Kreft et al. (2022)
1.0	3.5	46.9	Chang et al. (2021)
0.93	3.2	30.9	Kozakiewicz-Latała et al. (2022)
0.95	3.6	26.5	Wang et al. (2021)
1.01	3.5	46.9	Chang et al. (2020)
1.02–1.10	0.8–4.7	41.6–47.9	Wilts et al. (2019)

especially at the heater of thermal print heads that work by creating a bubble to eject the ink.

To predict the chance of success in jetting an ink from the print head, a dimensionless Ohnesorge (Oh) number is usually calculated using the following equation:

$$Oh = \frac{\eta}{\sqrt{\rho\sigma d}}$$

where d is the nozzle diameter, ρ is the ink's density, σ is the ink's surface tension, and η is the ink's dynamic viscosity, respectively. Physically, the Oh number represents a dimensionless viscosity that compares the relative importance of the inertia, surface forces, and viscous forces. An exceedingly high Oh number indicates the fluid motion and inertia created by the piezoelectric or heating elements within the print head may not be sufficient in overcoming the viscous and surface forces to result in jetting. Conversely, if the Oh number is too low, the jet may break up into tiny “satellite droplets”, resulting in drop placement errors (Guo et al. 2017). Empirically, an Oh number between 0.1 and 1 is desired for ink jetting, although the exact range depends on the print head of choice and actual jetting conditions (Derby 2010). Despite its popularity, Oh analysis also ignores non-Newtonian behavior and any elasticity of the ink that may manifest at high frequencies that are relevant to inkjet printing (Vadillo et al. 2010). Given the vast literature on inkjet technology, interested readers are encouraged to refer to several review papers and textbooks for more in-depth discussions and theoretical treatment on inkjet printing (Derby 2010; Hutchings and Martin 2013; Guo et al. 2017; Dijkman 2019). Table 10.3 summarizes the fluid properties of some of the liquid binders reported in the literature for pharmaceutical manufacturing. The viscosity is typically less than 10 mPa s. The surface tension is around 30–40 mN/m, which is typical for organic solvents. If water is used, surfactants are usually added to reduce the surface tension. Given the relatively high frequency and short characteristic time scale of the inkjet process, the dynamic surface tension which is influenced by the transport of surfactants to the air-liquid interface is more relevant compared to equilibrium values.

In terms of powder feedstock requirements, BJT works by spreading a layer of powder. Good flowability of the powder is required to ensure the powder can be

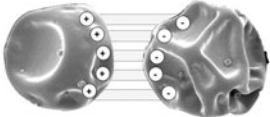
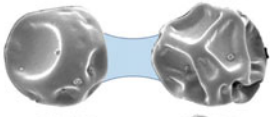
	Description	Illustration	Strength
Van der Waals	Temporary dipoles at powder particles interact via ionic bonding with dipole of closely located particles .		+
Electrostatic	Opposite charges on surfaces of powders from friction and attrition lead to ionic bonding between particles		++
Liquid bridging	Surrounding or internal moisture condenses at contact points between particles. Liquid capillary forces cause adhesion.		+++
Solid bridging	Solidification of liquid bridges via evaporation or crystallisation cause large increase in adhesion strength.		++++

Fig. 10.2 Summary of interparticle interactions. (Reproduced from Hazlett et al. 2021)

reliably discharged from the hopper (if any) and spread onto the build platform uniformly without resulting in major voids that will become defects and weak points in the printed products (Antic et al. 2021). In the case of a powder blend, the uniformity of the blend should be evaluated to make sure no unwanted segregation during the discharge and spreading processes. This is especially important if the API is included in the powder. Flow indices, such as Hausner ratio and Carr index, have been used as a guide to evaluate and rank different powder options (Abdullah and Geldart 1999; Ganesan et al. 2008; Schulze 2014; Chang et al. 2020; Kreft et al. 2022). In addition to the uniformity of the spread powder layer, the choice of powder will also affect the powder packing density which in turn influences the mechanical and drug release properties of the printed dosage forms.

Besides ink jettability and powder flowability, a key decision is how to pair the selected powder with the correct ink for successful binding. Relatively few studies directly address the detailed binding mechanisms, although some fundamental understanding has been established in the powder literature (Hazlett et al. 2021). Powders may be bound together by van der Waals and/or electrostatic interactions (Fig. 10.2). However, these interactions do not typically yield considerable strength which is required for maintaining the shape and mechanical integrity of the printed products. Calcium sulfate hemihydrate (CSH), also known as “plaster of Paris,” is typically used in BJP for rapid prototyping applications. CSH is also the main component in commercial BJP powders, sold under the trade name of VisiJet® PXL Core. As CSH is exposed to an aqueous ink, a highly exothermic reaction occurs, leading to the crystallization of gypsum and the formation of calcium sulfate dihydrate (Ridge et al. 1961). Several studies used this commercial powder and pharmaceutical-grade CSH in their experiments (Tables 10.1 and 10.2). Besides

CSH, lactose monohydrate (LMH) has also been used to produce solid dosage forms with breaking force and disintegration properties that are comparable to tablets creating from pressing (Chang et al. 2021). We hypothesize that as LMH is exposed to an aqueous ink, the powder is partially dissolved, forming liquid bridges between the powder particles. These liquid bridges are then transformed into solid bridges during subsequent drying process, creating considerable strength in the printed object (Adhikari et al. 2001; Hazlett et al. 2021). The binding mechanism is analogous to the wet granulation process, in which a liquid is sprayed onto the powder and then dried, except that the binding occurs layer-wise in BJT.

3 Hardware Considerations

Inkjet printing is a rather mature technology after its inception in the 1970s (Hutchings and Martin 2013). Inkjet printing can generally be classified as “drop-on-demand (DoD)” or “continuous inkjet (CIJ)” methods. As the names suggest, in DoD method, a drop is created as needed during printing, whereas a steady stream of drops is created continuously in CIJ. In CIJ, the drops are selectively deflected onto a print substrate as needed, and any non-deflected drops are recycled via a gutter. There are two types of DoD print heads, namely, piezoelectric print heads and thermal print heads. In a piezoelectric print head, an electrical waveform is sent to a piezoelectric transducer that results in acoustic waves and consequently ink displacements. In thermal print heads, a heater is included to locally heat up the ink, forming a vapor bubble that pushes the ink out of the nozzle. Regardless of the mode of operation, the pushing action must overcome the surface tension and pressure drop associated with the viscous flows for jetting to occur. A wide variety of print heads are commercially available to choose from, depending on the desired chemical compatibility, target drop size, and number of nozzles that is related to the throughput. Some of these print heads are originally designed for roll-to-roll operations, which is a great advantage for scaling up the BJP process. For small-scale operations, the print heads are typically mounted on a gantry or robotic system. For industrial scale print heads, the print heads are typically mounted fixed, while the build platform moves mainly because of the relatively larger weight and inertia of the entire print head assembly that consists of an ink supply and recirculation system and the drive electronics (Chang et al. 2021). In BJT, powders are usually stored in a gravity-fed or vibratory hopper, discharged onto the powder bed using an auger, and spread using a blade or roller. A compaction roller may also be added to increase the powder particle packing after spreading. For pilot-scale production, an alternative design is to use a two-elevator system, whereby a feed platform holding the powder moves up under a roller that pushes the powder onto a build platform, as reported in (Chang et al. 2021).

4 Process Considerations

The level of liquid binder saturation is defined as the mass ratio between the liquid binder to powder and is one of the most important process parameters in BJT. There is a strong correlation between the level of binder saturation and the final properties of the printed dosage forms in terms of breaking forces and disintegration times (Chang et al. 2021). The total amount of liquid binder depends on the binder's fluid properties, print head design (mainly nozzle size), and jetting conditions. The amount of binder can be quantified by jetting into a weighing boat. Multiple rounds of jetting may be needed to reduce measurement error in weighing. In piezoelectric print heads, an electrical waveform is used to control the jetting action. Key process parameters include the firing voltage, pulse width, and frequency. The firing voltage should be sufficiently high to impart enough energy for overcoming pressure drop and surface forces. However, too high an energy may result in instability and formation of satellite drops. The optimal pulse width depends on the acoustics within the print head, which is largely determined by the geometric design of the print head and the speed of sound through the ink (Dijksman 2019). The selection of voltage and pulse width will affect the actual drop volume and drop velocity (Lin et al. 2006; Kwon 2010). High-speed or stroboscopic imaging techniques have been successfully used to visualize the jetting and to optimize the jetting waveform experimentally (Hoath et al. 2013, 2014). Theoretically, the coupling between fluid properties and print head design is intriguingly complicated but may be understood by solving the equation of motion and modeling the print head as Helmholtz resonators (Dijksman 2019). In practice, different machine learning approaches have also been used to optimize the jetting waveforms (Wang et al. 2018; Zhang et al. 2019; Ruberu et al. 2021; Brishty et al. 2022).

In terms of powder spreading, the roller or blade design, together with the spreading rate, affects the final powder packing density. Powder flow experiments may be carried out to understand the cohesiveness of the print powder (Antic et al. 2021), but unlike tableting, little compaction force is exerted during the powder spreading. As the liquid binder is deposited onto the powder bed, the penetration and lateral spreading of the binder further depend on the amount of binder deposited, the porosity of the powder bed, and wettability of the powder. Certain powders may also dissolve or swell in the presence of the liquid binder. As a quick screening method, a drop of the liquid ink may be casted onto the powder bed (Antic et al. 2021; Sen et al. 2021b; Kozakiewicz-Latała et al. 2022). To determine how thick a fresh layer of powder to be spread (build layer thickness, l_b), it is useful to print a single layer and measure the thickness of a single printed layer (d_p as shown in Fig. 10.3) (Chang et al. 2021). l_b should be chosen such that it is small enough to ensure good overlap between the printed layers, but sufficiently large such that the previously printed layer is not sheared or shifted by the powder spreading action. Dividing d_p by l_b gives a dimensionless parameter termed the “degree of overlap” (DO). A DO between 1 and 2 is empirically found to be desirable for maximizing mechanical strength and maintaining shape fidelity (Chang et al. 2021).

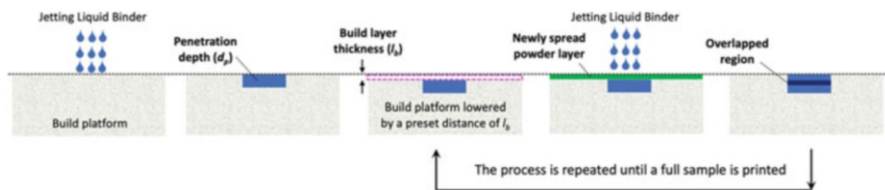


Fig. 10.3 A schematic diagram outlining the BJT mechanism and two key parameters, namely, the penetration depth (d_p) and build layer thickness (l_b). (Reproduced from Chang et al. 2021)

5 Properties of Fast-Disintegrating and Sustained-Release Printed Dosage Forms

Tables 10.4 and 10.5 summarize the key attributes of the fast-disintegrating and sustained-release 3D printed dosage forms, respectively. A wide range of breaking forces have been reported, but with proper material selection and process optimization, the mechanical properties of 3D printed dosage forms are comparable with commercial tablets (Katstra et al. 2000). However, the friability of these dosage forms tends to be much higher than that of commercial tablets ($< 1\%$). This is probably because of the lack of compaction during the printing process and/or insufficient removal of loose powder from the surface of the printed dosage forms during post-processing. The friability, although higher compared to current industry standard, may still be acceptable for point-of-use applications. For sustained-release dosage forms, the drug release time scale varies greatly as shown in Table 10.5, depending on the formulation and retardation mechanism. Considerable number of studies focused only on the drug release and did not report the breaking forces or friability.

6 Challenges and Future Outlook

BJT is the first 3D printing method that has been approved by FDA for manufacturing solid dosage forms. BJT is founded on inkjet printing technology which is scalable and mature. The room temperature operation also makes it a desirable method for heat-sensitive API. However, BJT also has its limitations. First, the liquid ink must be chemically compatible and consistently jettable with the print head. Such requirements limit the choice of materials that can be introduced via the print head (Guo et al. 2017). While small drug molecules may be included in the ink and jetted, high molecular weight drugs may not be jetted in sufficient quantities as the associated viscosity will likely be too high. Particle dispersions are equally challenging to jet as they modify the jetting behavior and may clog the print head nozzles. Second, the lack of powder compaction means that BJT tends to produce dosage forms with high porosity (Chang et al. 2021). Although beneficial for increasing the mass transfer in fast disintegrating applications, the high porosity may limit the mechanical integrity and sustained release applications. Third,

Table 10.4 Reported properties of fast-disintegrating BJT solid dosage forms

Breaking force (kgf)	Friability	Disintegration time	References
0.31–0.82	41.15–97.24%	4–24 s	Kreft et al. (2022)
9.4	2.5%	8 s	Chang et al. (2021)
4.64–15.49	0.47–0.70%	55–84 s	Kozakiewicz-Latała et al. (2022)
2.15–6.04	2.77–5.75%	9–17 s	Wang et al. (2021)
2.65–26.73	3.3–21.5%	6–1447 s	Wang et al. (2022)
ca. 6	–	<30 s	Wilts et al. (2019)
ca. 4	0.92%	21.8 s	Yu et al. (2009a, b)

Table 10.5 Reported properties of sustained-release BJT solid dosage forms

Breaking force (kgf)	Friability	Time for 80% of the drug released	References
–	–	Ritonavir: 180 min Favipiravir: 250 min	Lu et al. (2022)
–	–	4–10 h	Rowe et al. (2000)
7–17	1.05%	40 min–6.5 h	Katstra et al. (2000)
–	–	6–13 h	Wang et al. (2006)
7.5	0.27%	3–10 h	Yu et al. (2007)
–	–	5–80 days	Huang et al. (2007)
5.3–8.8	0.37–1.21%	6–9 h	Yu et al. (2009a, b)
–	0.94–2.47%	21–47 min	Infanger et al. (2019)
3.5–12.5	4.2–16.3%	1.8–3.5 h	Tan et al. (2023)

considerable amount of powder is used in BJT as the powder is generally spread across the entire build platform (Gibson et al. 2021). This may limit clinical trial applications where only small quantities of API are available. For larger-scale manufacturing, the reclaim and reuse of powder without contamination must also be addressed. The relatively slow drying and recovery of as-printed products from the powder bed remain the bottleneck for increasing the throughput. We foresee these challenges will remain active areas for research, leading to further material and process innovations that will unlock the full potential of BJT for pharmaceutical manufacturing.

Multiple Choices

- Which of the following sentences accurately describe the binder jetting (BJT) process according to ASTM F2792?
 - An additive manufacturing process in which material is selectively dispensed through a nozzle or orifice
 - An additive manufacturing process in which a liquid bonding agent is selectively deposited to join powder materials
 - An additive manufacturing process in which thermal energy selectively fuses regions of a powder bed

- D. An additive manufacturing process in which liquid photopolymer in a vat is selectively cured by light-activated polymerization
- E. An additive manufacturing process in which droplets of build material are selectively deposited

Correct answer is “B.” “A” describes “material extrusion”; “C” describes “powder bed fusion”; “D” describes “vat photopolymerization”; and “E” describes “material jetting.”

2. Which of the following attributes is *not* an advantage of binder jetting?
- A. Suitable for handling heat-sensitive ingredients
 - B. Support the printing of overhang structures
 - C. Suitable for selective deposition of high molecular drugs
 - D. Suitable for producing highly porous dosage forms that quickly disintegrate
 - E. Scalable

Correct answer is “C.” High molecular drugs are difficult to jet due to high viscosity.

3. Which of the following fluid parameter(s) affect the jettability of a liquid binder?
- A. Viscosity
 - B. Surface tension
 - C. Density
 - D. Speed of sound
 - E. All of the above

Correct answer is “E.”

4. Which of the following interparticle interactions has the highest strength as binding mechanism?
- A. Van der Waals
 - B. Electrostatic
 - C. Liquid bridging
 - D. Solid bridging

Correct answer is “D.”

5. Which of the following scenarios will likely result in the formation of satellite droplets that are undesirable?
- A. Low surface tension
 - B. High viscosity
 - C. Low density
 - D. High firing voltage

Correct answer is “D.” Exceedingly high firing voltage imparts too much energy that further promotes instability and droplet breakup. “A,” “B,” and “C” all result in a high Ohnesorge number. Satellite drops are less likely to form, but jetting may not occur.

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Chapter 11

Powder Bed Fusion 3D Printing in Drug Delivery



Wessel Kooijman and Julian Quodbach

Abstract Selective laser sintering (SLS) is a powder-based additive manufacturing technology. In SLS, the energy of a laser is utilized to locally fuse thin powder layers together to obtain three-dimensional objects. The combination of starting material in powder form and a heat-based fusion mechanism make SLS a highly interesting technology for the manufacturing of (individualized) medication. In this chapter, we will introduce the fundamental printing principle and process parameters. We will discuss how process parameters influence the printed dosage form, and we will elaborate on what material attributes are critical for robust, high-quality printing. We will highlight the unique capabilities of SLS and its potential for mass customization of medication.

Keywords Powder bed fusion · Selective laser sintering · Powder bed · 3D printing · Amorphous solid dispersions · Drug delivery · Personalized medicine

1 Introduction

Powder bed fusion (PBF) is, just like additive manufacturing, an umbrella term that comprises different technologies that are usually referred to as *sintering* technologies. In 1986, Carl Deckard submitted the patent application “Apparatus for producing parts by selective sintering” (Deckard 1986), which became a landmark in additive manufacturing history. It describes the layer-wise manufacturing of parts from powder materials using an energy source, in this case, a laser, to fuse the particles to defined agglomerates or objects. This is still the common denominator for all PBF technologies. Since then, a variety of different technological subcategories have been developed. The selection of printing material defines the type of energy source and thereby the technology to employ. While metal powders can be printed with lasers or electron beams, polymers and ceramics are usually processed

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with lasers only. When lasers are employed, the respective technology is called laser sintering (LS) and in the case of polymers polymer laser sintering (pLS) or selective laser sintering (SLS). For pharmaceutical applications, only polymers and other low-melting thermoplastic materials are applied. This chapter will consequently only cover SLS and pLS. In the remainder of the chapter, we will only use the term SLS.

Medical therapies are constantly changing and the speed of change has increased drastically. The understanding of physiological and disease mechanism has greatly improved within the past decades. Paired with novel diagnostic approaches, implementation and exploitation of big (biological) data sets and advances in pharmacogenetic analyses have led to novel therapies and therapy regimens that require individualized medication. While distributed, point-of-care manufacturing approaches, i.e., additive manufacturing in hospital and community pharmacies, can provide individualized medicines at therapy initiation, for dose titration and acute treatments, large-scale manufacturing of individualized dosages for prolonged treatment will require industrial translation. Mass customization cannot be realized with all 3D printing technologies, and some are more suitable than others. For this purpose, special attention has to be given to SLS.

The underlying processes, powder transfer, and powder melting are already well established in other large-scale pharmaceutical manufacturing processes. This familiarity makes the process more approachable for scientists. SLS is also one of the most advanced AM technologies. Companies have developed machines for specialty manufacturing that are widely employed across industries also for the manufacturing of high-performance parts. With such industrial deployment arose the interest for processing larger powder volumes, which resulted in the development of machines with high capacity. Machines with multiple laser systems and print volumes >100 l are available that demonstrate the scalability of this technology. Even though these machines were not developed to meet cGMP requirements, the technological feasibility has been demonstrated. SLS is therefore a prime candidate to enable industrial mass customization of medicines.

In this chapter, we will introduce the process and highlight the critical process parameters. We will discuss material requirements and how material properties manifest in the printed object. Lastly, we will highlight research that demonstrates the capabilities of SLS in the manufacturing of medicines.

2 The Technique

There are many different SLS printing systems that all slightly deviate from each other. To give a simple description of the workflow, we describe a generic SLS system as illustrated in Fig. 11.1. To start the printing process, the building plate lowers by a selected layer height, while the powder reservoirs move up by a set distance. The roller recoater then spreads a layer of powder from the powder reservoir over the building plate. The powder layer is heated up to a set temperature

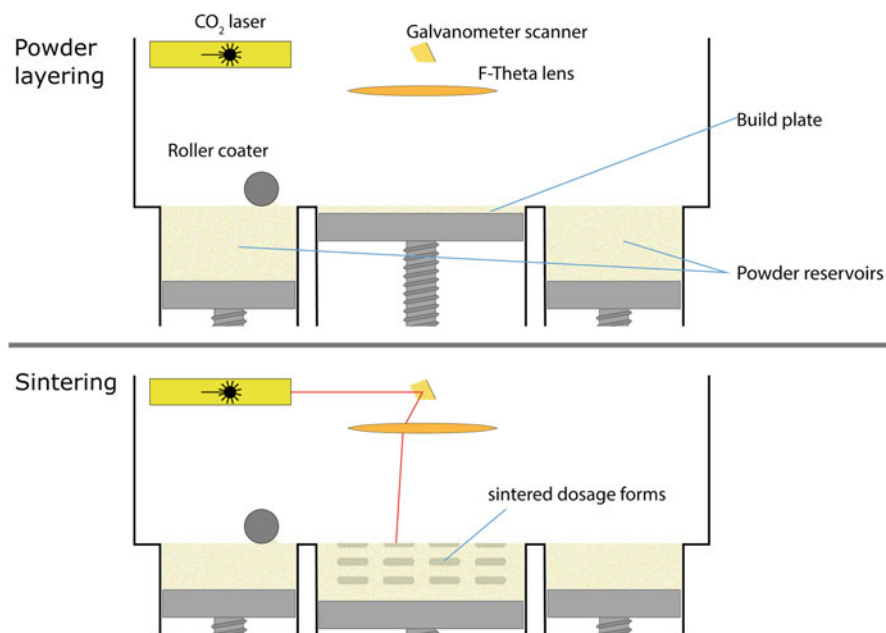


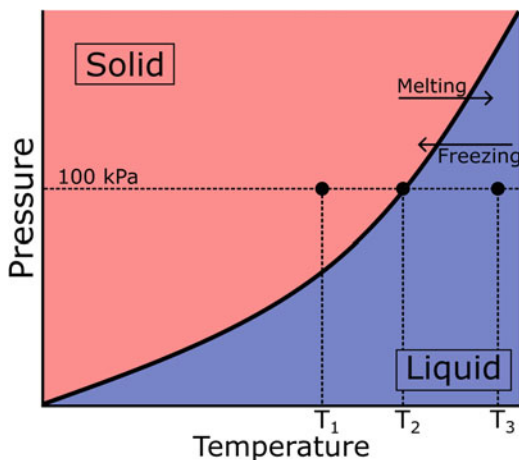
Fig. 11.1 Schematic drawing of SLS equipment and SLS 3D printing process

via infrared radiation. A laser now scans over a cross-sectional area generated from the 3D model that shall be printed and the laser energy fuses the particles together. The laser is usually moved over the surface using a galvanometer and is often focused with an F-theta lens. The powder surface is preheated to limit the necessary laser power to fuse the material. After the laser is finished scanning the layer, the building plate, powder reservoirs, and roller recoater are moved again to create the next powder layer. The laser can now again scan the surface fusing the fresh powder layer. These steps are repeated until the 3D object is completed. When the printing process is finished, the printed object is embedded in a block of unsintered powder. The block of powder should be allowed to slowly cool down to prevent thermal stress-induced deformations and defects. The unsintered powder acts as support material for the layers making support structures obsolete. After cooling, the 3D object can be retrieved from the powder block by brushing away the unsintered powder. The unsintered powder may be recycled for further prints (see Sect. 5.5).

3 Fusion Mechanisms

To create objects from powder, the powder has to be solidified via the energy input from the laser. While the name *selective laser sintering* implies that sintering is the main mode of powder fusion, this is not the case. Generally, four different fusion

Fig. 11.2 Phase diagram of a thermoplastic binder depicting the locations of sintering (T_1), partial melting (T_2), liquid phase sintering, and full melting (T_3)



mechanisms are distinguished. In a phase diagram of a thermoplastic binder material, three of these mechanisms can be located (Fig. 11.2). At T_1 , below the material's melting temperature in a solid state, sintering takes place. At T_2 , on the boundary between the solid and liquid state, partial melting occurs, and at T_3 , liquid phase sintering and full melting take place. Liquid phase sintering and partial melting are often not properly distinguished because of similarities that will be discussed in Sect. 3.2. The fourth mechanism, chemically induced sintering, is at present irrelevant in pharmaceutical processes and will only be described briefly.

3.1 Solid-State Sintering

Traditionally, sintering describes the process of material fusion at elevated temperatures, which occurs approximately between half the absolute melting point and the melting point. In this temperature range, powder particles can spontaneously fuse together without transition to the liquid state. The driving force behind this process is a decrease in total interfacial energy, γA . The total interfacial energy is noted as γA , where γ is the specific surface energy and A is the total area of the powder compact. The change in the total interfacial energy can be expressed using Eq. 11.1 (Kang 2005):

$$\Delta(\gamma A) = \Delta\gamma A + \gamma \Delta A \quad (11.1)$$

The first term, $\Delta\gamma A$, is related to the densification of the powder. As can be seen in Fig. 11.3, solid-gas interfaces are replaced with solid-solid interfaces. As solid-solid interfaces have a smaller specific surface energy than solid-gas interfaces, the total specific surface energy decreases and therefore also the total interfacial energy. The second term, $\gamma \Delta A$, is related to the coarsening of the powder. When powder particles

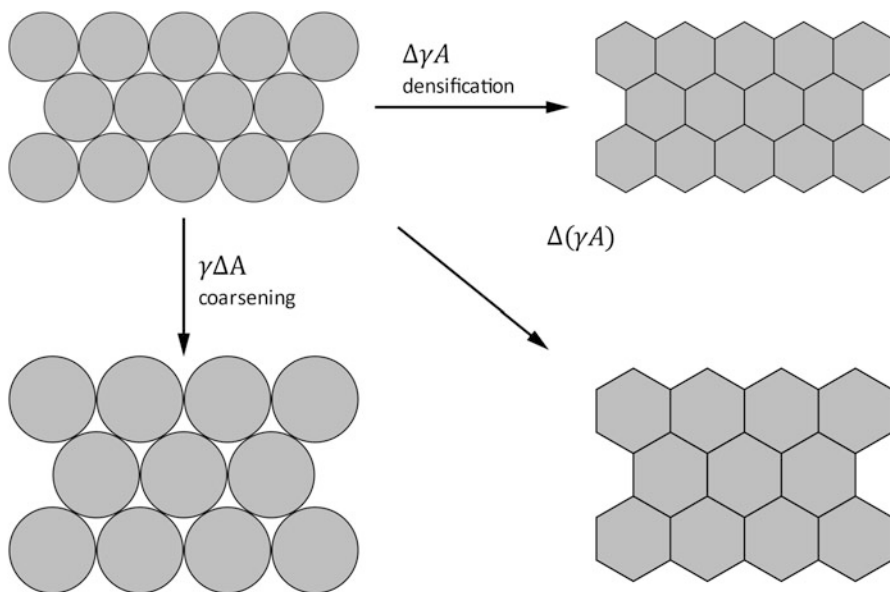


Fig. 11.3 Schematic drawing of densification and coarsening caused by sintering

agglomerate into bigger particles, the total surface area decreases and thus the total interfacial energy. The decrease in specific surface energy and particle growth are the driving forces behind solid-state sintering (Kang 2005).

This also explains why smaller particles are more suitable for sintering than larger particles. The inherent driving force, the total interfacial energy, is higher for small particles. Conversely, the energy input has to be increased, either by longer sintering time, higher powder temperature, or higher laser power, to obtain a similar degree of fusion with larger powder particles. With progressing sintering and particle agglomeration, the fusion rate decelerates, as the total interfacial energy decreases. To further reduce porosity, sintering times have to be prolonged or higher temperatures have to be employed.

The sintering rate clearly increases with temperature. Sintering close to the melting temperature is much faster than sintering at half the melting temperature. Even close to the melting temperature, solid-state sintering is comparably slow and only plays a minor role in powder bed fusion. Selective laser *sintering* is therefore a misnomer as other fusion mechanisms are more relevant.

While sintering plays only a minor part in the wanted aspects of powder fusion, it is the reason for several unwanted observations during SLS printing. With ongoing printing time, slowly progressing sintering can cause the formation of a porosity gradient along the z-axis with lower porosities in the sections at the bottom that were printed first. It may be possible that, when multiple layers of dosage forms are stacked on top of each other in a single print job, the dosage forms at the bottom have a lower porosity than the ones on top. This should be investigated as the porosity

influences interaction with liquid media, i.e., gastric and intestinal fluid, and thereby influences disintegration and dissolution mechanisms. Another effect of sintering is the unwanted agglomeration of powder in the powder bed that should not agglomerate. A modified (larger) particle size distribution will change the powder spreadability and potentially lead to different quality attributes of the final dosage form. This may impede powder recycling. Another undesired effect is the growth of printed parts because of sintering. The 3D printed part has a higher temperature than the surrounding powder, inducing additional sintering at the object-powder interface. This can be factored into the printing process but may result in dosage forms of lower surface quality.

3.2 Liquid Phase Sintering and Partial Melting

Liquid phase sintering describes the fusion of powder particles in a powder mixture where only parts of the mixture melt and cause the intended agglomeration. During liquid phase sintering, solid particles and a molten liquid coexist, and the molten liquid acts as binder between the solid grains. In multicomponent mixtures, a low-melting binder can be combined with a high-melting material (or drug), resulting in the formation of solid bridges between the high-melting grains as shown in Fig. 11.4. Frequently, the fusion process stops at the stage depicted in Fig. 11.4b, and the consolidation caused by capillary forces shown in Fig. 11.4c does not take place. In such cases, objects with higher porosity are obtained.

A fundamental requirement for the formation of a sturdy construct is wetting of the solid material by the liquid binder. Furthermore, capillary forces that draw liquid binder into pores are also important for the distribution of the liquid. Materials are considered to be partially wettable when the contact angle θ between solid and liquid is $0 < \theta < 90^\circ$ and completely wettable when $\theta = 0^\circ$ (Fig. 11.5).

Wettability depends on the interfacial energies between existing phases. At the moment of liquid formation during liquid phase sintering, solid, liquid, and vapor phases coexist, and, consequently, three interfacial energies, γ_{SL} , γ_{SV} , and γ_{LV} (S , L ,

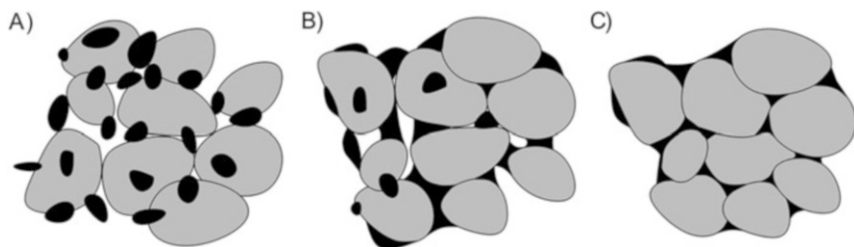


Fig. 11.4 (a) Powder mixture consisting of binder (black) and structural material (gray); (b) melting and spreading of binder; (c) consolidation of particles caused by capillary forces and final printed part

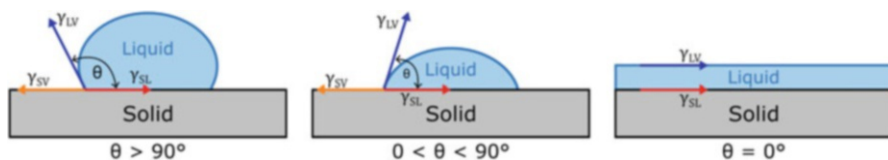


Fig. 11.5 Depiction of contact angles of poorly wetting liquids (left), wetting liquids (middle), and fully spreading liquids (right)

and V denoting the solid, liquid, and vapor phases), determine the contact angle between liquid and solid. This relationship is expressed by Eq. 11.2 (Bachmann and McHale 2009):

$$\theta = \arccos\left(\frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}}\right) \quad (11.2)$$

A liquid with a low contact angle θ , i.e., a liquid that readily wets the surfaces of embedded particles, provides a capillary force that draws the particles closer together, thereby supplementing the densification of the sintered part (Fig. 11.4c). Even though the extension of the capillary effect can be calculated as it depends on the amount of liquid, particle size, and contact angle, it is difficult to apply for pharmaceutical SLS. Traditional powders for SLS are highly spherical, often nonporous, and have a narrow particle size distribution, simplifying calculations. In contrast, pharmaceutical materials are more diverse. They are rarely spherical, have highly irregular surface structures and varying porosity, which complicates calculations. Additionally, particle size distributions are frequently broad further reducing the applicability.

Liquid phase sintering is a main fusion mechanism for different powder compositions, and four distinct cases are distinguished (Kruth et al. 2005). In Fig. 11.6, these cases are depicted. In case 1, the binding material is distinct from the structural material. Only the binder melts and causes fusion of the material. In case 2, composite particles are shown where particles consist of a lower melting binder and of non-melting structural material. Structural particles can also be coated with a binder (case 3). The last case, case 4, depicts a material that can serve as binder and structural material at the same time. In this case, only sections of the particles melt and cause fusion, whereas the remaining sections of the particles remain solid. This is also known as partial melting. In the phase diagram in Fig. 11.2, liquid phase sintering and partial melting are located at different positions, indicating different phase behaviors. However, the underlying fusion processes are similar, and they are often not specifically distinguished.

In pharmaceutical SLS, the presence of separate binding and structural materials (case 1) is the most prominent. In the simplest situation, a binary mixture of only a polymeric binder with a non-melting drug substance is utilized. No preprocesses except blending are necessary to obtain the desired formulation. However, such mixtures have a more complex behavior than powder consisting only of one species.

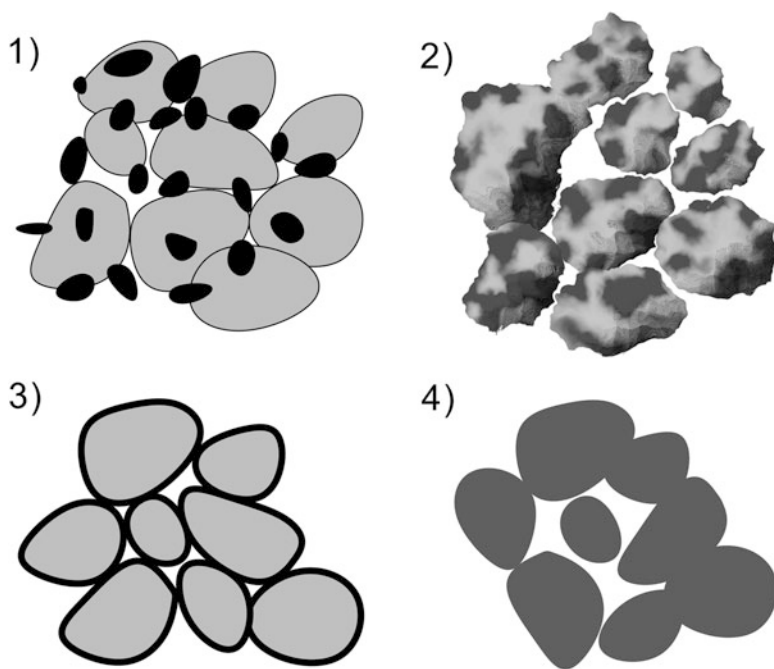


Fig. 11.6 Liquid phase sintering variations utilized in SLS according to Kruth et al. (2005): (1) separate binding and structural materials; (2) composite particles; (3) coated particles; (4) separate binding and structural materials; black, binding material; light gray, structural material; dark gray, partially melting material

They can de-mix, leading to uneven drug distribution in the powder bed and may not show sufficient flowability and spreadability for robust processing. Co-processed, composite particles and coated particles (cases 2 and 3) will not show de-mixing but require preprocessing and further equipment such as fluidized bed processors, spray driers, or dry compaction units. Additional development is necessary to obtain such materials but advantages, for example, the options to reduce the binder content or incorporate drug directly in the particles, may make it worthwhile. The presence of mostly homogenous, single-species particles that partially melt and form a fused powder bed (case 4), represents the least likely situation in pharmaceutical SLS. In this case, the drug substance itself will have to serve as a (partial) binder, or the dosage form will only consist of a given excipient. Even though this is not the most likely case, this is indeed a possibility as will be shown later.

A situation not considered in common (industrial) applications is the change of the solid state of additional particle species during liquid phase sintering. This is especially relevant for the incorporated drug substances. Drug substances with melting temperatures close to the melting or glass transition temperature of the thermoplastic binder can also melt in SLS. After melting and upon cooling, the drug may recrystallize or form an undercooled, amorphous melt. Melted drug may

even dissolve in the binder and form an amorphous solid dispersion. The formation of the amorphous state can be exploited to increase the dissolution rate of poorly soluble drugs (Van de Mooter [2012](#); Davis Jr. et al. [2021](#)).

3.3 *Full Melting*

When the energy input is high enough and the powder has sufficient thermal conductivity, the particles in the current layer and parts of the previously printed layer can melt fully. This process is coined *full melting* and is often associated with semicrystalline polymers and metal alloys. When the complete irradiated material section and part of the underlying structure melt, high part density and very well bonded objects are obtained. To ensure sufficient energy input, the powder bed is usually heated to just below the melting or glass transition temperatures of the powder material. This leads to a prolonged energy input and object growth because of sintering (see Sect. [3.1](#)). In non-pharmaceutical applications, this may be sensible when high mechanical strength is important and post-processing, e.g., milling down to the desired dimensional specification, is possible. For the manufacturing of medicines, post-processing should be limited to thorough dedusting and further modification of the dosage forms avoided. Full melting should, thus, be avoided unless the dosage form growth is highly reproducible and can be considered during dosage form design.

3.4 *Chemically Induced Sintering*

Chemically induced sintering utilizes thermally induced chemical reactions to form a reaction product between atmospheric gases and powder particles or between different types of powders. The in situ formed reaction product causes fusion of the particles. Different ceramics are fused via this mechanism, but no pharmaceutical applications have been described, yet. The development of formulations following this approach is likely complicated. As quantitative reactions cannot be guaranteed, high safety requirements have to be fulfilled by the starting materials. Excipients have to be nontoxic prior to and after fusion, and intermediate products have to adhere to the same requirements. If this is not attainable, other measures to ensure a sufficient safety profile of the powder have to be taken.

4 Process Parameters

SLS printing is a complex, multidimensional process where the process parameters and material parameters depend on each other. We will discuss the most important process parameters and follow up with a discussion of the material properties. The process parameters can be placed in two distinct groups, the laser parameters and the building parameters (Table 11.1). The laser power, scanning speed, hatch spacing, and layer height are all parameters that directly influence the energy transfer from the laser to the surface. That is why these parameters are discussed together under the section energy density (Sect. 4.1.2). The layer height is also discussed separately (Sect. 4.2.1).

4.1 Laser Parameters

4.1.1 Wavelength λ

In literature, two types of lasers are commonly used for the printing of pharmaceutical dosage forms, namely, CO₂ lasers (Gueche et al. 2021a) and diode lasers (Gueche et al. 2021b; Fina et al. 2017). Diode lasers are more prevalent as they are comparably cheap, and the equipment has a small footprint. Frequently, a blue diode is utilized. Light from blue diodes ($\lambda = 445\text{--}450\text{ nm}$) is absorbed in the visible spectrum. Because most pharmaceutical excipients and drug substances are colorless, they cannot absorb the emitted laser energy. The light absorbance can be increased by adding an absorbent to ensure that the powder mixture absorbs the blue diode laser light. Absorbents used in pharmaceutical studies are usually pigments, e.g., Candurin® gold sheen or Candurin® NXT Ruby Red (Fina et al. 2017; Awad et al. 2020; Barakh Ali et al. 2019). Usually, only low quantities below <5% are added, which means that only 5% of the formulation may absorb energy, resulting in a low conversion of laser to thermal energy.

CO₂ lasers are more expensive compared to diode lasers but have advantages over diode lasers that make them interesting for pharmaceutical applications. The laser light of a CO₂ laser has a wavelength of $\lambda = 10.6\text{ }\mu\text{m}$ and is readily absorbed by most organic molecules. This is an advantage as there is no inherent need for an

Table 11.1 Main process parameters in SLS 3D printing

Group	Parameter	Description
Laser parameters	Laser power	Power output of the laser
	Wavelength	Wavelength of the sintering laser
	Scanning speed	Speed at which the laser scans the surface
	Hatch spacing	Distance between two parallel laser paths
Building parameters	Layer height	Height of individual powder layers
	Printing temperature	The temperature of the powder bed while printing

absorbent. Since all or most of the powder mixture serves as energy absorbent, conversion of laser to thermal energy is more efficient, and printing at lower printing temperatures should be possible. A potential benefit for higher printing speeds is that the power output of a CO₂ laser can be significantly higher than the power output of a diode laser.

4.1.2 Energy Density

Fusion of the powder does not solely depend on the laser power but mainly depends on the so-called energy density. The energy density can be described with the following empirical equation (Eq. 11.3):

$$ED = \frac{P_L f}{v_s d_L h_s} \quad (11.3)$$

ED is the energy density (J mm^{-3}), P_L is the laser power (W), f is the absorptance of the powder, v_s is the laser scanning speed (mm s^{-1}), d_L is the layer thickness, and h_s is the hatch spacing (mm) (Fig. 11.7) (Ho et al. 1999; Drummer et al. 2010). The hatch spacing is the distance of parallel scanning lines of the laser. It can be seen that in order to increase the energy density, it is possible to increase the laser power, but it is also possible to decrease the scanning speed, hatch distance, or layer thickness.

A sufficient energy density is required to melt the binder material in a pharmaceutical mixture. Depending on the energy density, liquid phase sintering or full melting will result as depicted in Fig. 11.8a. The energy density should be high enough to (partially) melt the new and unsintered powder layer and part of the layer beneath it to ensure proper layer layer adhesion. With a too low energy density,

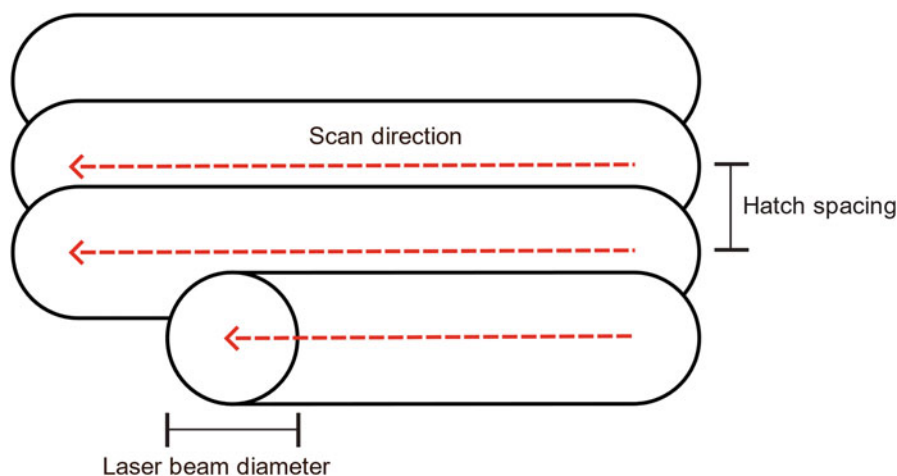


Fig. 11.7 Illustration of a laser path

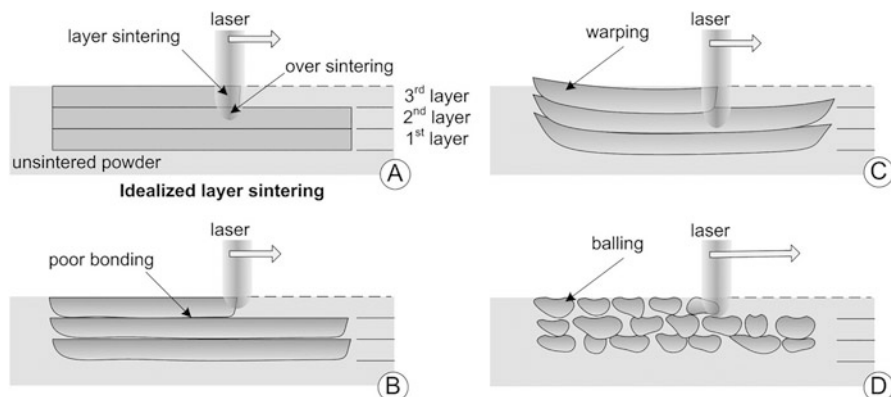


Fig. 11.8 Different effects of variation in laser energy density. (Reprinted from Beal et al. (2009) with permission from Springer)

delamination can occur because the laser can only melt a part of the first layer causing poor adhesion between the layers (Fig. 11.8b). Delamination leads to poor mechanical strength of the printed part, and the layers might even separate from each other during printing causing the print to fail.

With excessive energy density, warping might occur as shown in Fig. 11.8c. The term warping is used to describe the deformation of a print because of thermal stresses within the printed structure or between printed structure and surrounding powder during printing and cooling. With a low degree of warping, the print can still be completed, and the resulting dosage form will only be slightly distorted. With a high degree of warping, however, the curled-up part will be dislodged by the recoater removing it from the desired location causing print failure. In Fig. 11.8d, a printing process is depicted where the laser power and scanning speed are both excessive. This results in balling, the local fusion of powder without formation of a coherent structure. Balling results in a rough surface and leads to cracks and high porosity. In most applications of SLS, these are unwanted characteristics. For pharmaceutical applications, a high porosity might be beneficial as it might promote drug dissolution and tablet disintegration.

According to Eq. 11.3, the same energy density can be obtained for different input parameters. When the laser power and scan speed are both doubled, the energy density remains unchanged. The sintering process however might change from idealized layer sintering (Fig. 11.8a) to a process with severe balling (Fig. 11.8d). This change in sintering cannot be explained with Eq. 11.3, and the outcomes of the equation should therefore always be considered within the context of the printing process.

4.2 Building Parameters

4.2.1 Layer Height

The layer height is an important parameter for the printing process. It partly determines the resolution of the printed object but is also inversely correlated to the printing time. The layer height has not only to be chosen carefully because of the printing time but also because of the penetration depth of the laser. If it is set too high, the laser beam will not penetrate the complete layer resulting in incomplete melting and poor layer adhesion. Too low layer heights (usually considered to be $<80\text{ }\mu\text{m}$) can also cause problems when the particle size of the powder exceeds the layer height. If the particle size is larger than the layer height, powder spreadability issues will occur as particles will be dragged by the recoater and not form a smooth layer. The selected layer height is, thus, material dependent and depends on particle size distribution, powder density, particle shape, powder compactability, thermal conductivity, and specific heat of the material. As rule of thumb, layer height for SLS printing lies in the range of 100–150 μm (Goodridge and Ziegelmeier 2017). For pharmaceutical blends, this might not be easily achieved as the median particle size of many excipients exceeds 150 μm . In cases where limited laser penetration depth interferes with the particle size, the powder may have to be milled or sieve fractions have to be used.

4.2.2 Printing Temperature

The powder bed temperature is the temperature of the powder surface on the building plate. Control of the surface temperature is of utmost importance to obtain high-quality prints. Either the surface temperature is measured and controlled directly, or the environmental temperature, the temperature inside the build chamber, is measured as surrogate. The surface temperature is usually measured with an IR sensor. Controlling the powder surface temperature is critical for the sintering process because the energy density required to properly fuse the powder is significantly reduced by preheating the powder. For amorphous polymers, the powder bed temperature is usually set to just below the glass temperature T_g . For semicrystalline polymers, the bed temperature depends on the degree of crystallinity. Semicrystalline polymers with large crystalline domains are typically set to a powder temperature of 3–4 °C below the melting point T_m of the material. Semicrystalline polymers with smaller crystalline domains may require powder bed temperatures slightly below their T_g (Awad et al. 2020). Controlling the powder bed temperature via measurement of the surface temperature is more accurate as newly created powder layers may have a lower temperature than the preset one. In this case, printing can be interrupted until the proper powder temperature is reached. This is not possible when only the chamber temperature is measured.

5 Material Attributes

When printing medicine, all formulation constituents are selected to accommodate the drug substance. It is crucial that the drug does not degrade when exposed to elevated temperatures for prolonged periods of time (hours). When utilizing a diode laser, prolonged heating of the powder bed is a necessity because of the low energy conversion efficiency due to the low colorant concentration. With a CO₂ laser, low-temperature printing may be possible, but the drug still has to withstand the laser pulse during the fusion process. In industrial application, the build chamber is often flushed with inert gases such as nitrogen and argon to prevent oxidative degradation. It appears sensible to implement this in pharmaceutical manufacturing as well.

The drug substance can be blended with a wide variety of excipients to improve the physicochemical properties of the resulting formulation. For robust and reliable SLS printing, formulations need to fulfil certain properties. These properties can be divided into extrinsic and intrinsic properties. Intrinsic material properties are properties that are related to the molecular structure of a material, for example, melting and glass transition temperature, absorptance, melt viscosity, or surface tension. Extrinsic material properties are used to describe the physical behavior of particles and powders such as powder flowability, particle shape and size, or packing density (Table 11.2). In this section, we will elaborate on the different desired properties of the printing blend and how certain excipients can influence these.

5.1 Thermal Properties

As mentioned before, SLS requires the use of thermoplastic materials as a binder. Thermoplastic materials are characterized by their ability to soften upon heating and solidification after cooling without changing chemically. Usually, polymers are used for this purpose. Polymers that have been used for pharmaceutical SLS are, for example, Kollidon® VA64 (Barakh Ali et al. 2019), Eudragit® L100-55 (Fina et al. 2017), and Kollicoat® IR (Gueche et al. 2021b; Hamed et al. 2021). The powder bed

Table 11.2 Intrinsic and extrinsic powder properties relevant for SLS 3D printing

	Group	Examples
Intrinsic	Thermal	Melting temperature, glass transition temperature, molecular diffusion, sintering window
	Interaction with radiation	Absorption bands of blend constituents
Extrinsic	Bulk level	Flowability, compactability, spreadability, particle size distribution, powder recycling
	Particle level	Particle shape and surface structure, agglomerated or monolithic particles

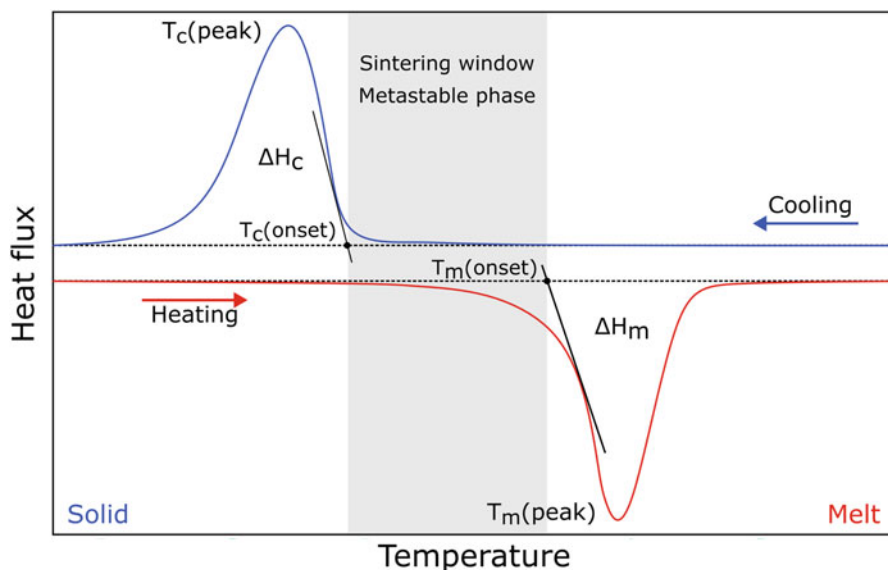


Fig. 11.9 Thermogram of semicrystalline polymers showing melting and recrystallization events and the sintering window; T_g not shown

temperature is dependent on the thermal characteristics of the thermoplastic polymer. Amorphous polymers do not have a melting point but a glass transition temperature T_g above which they become increasingly soft with an increase in temperature. The powder bed temperature should be set slightly below the T_g of the polymer. This limits the required energy input by the laser. Semicrystalline materials have a T_g and a melting temperature T_m . Figure 11.9 shows a differential scanning calorimetry (DSC) measurement of a generic semicrystalline polymer. In the thermogram, a sample of the semicrystalline material is heated and cooled, and the phase transition energies are displayed. The melting point of the material corresponds to the onset temperature of the melting peak.

During cooling, recrystallization does not happen at the same temperature as melting. The crystallization temperature $T_c(\text{onset})$ occurs at a lower temperature. The temperature region between T_c and T_m is metastable and molten and solid material can coexist. In SLS, this zone is called the sintering window of a given material. In practice, the powder bed temperature is set slightly below T_m , and the laser provides the necessary energy for melting. For printed parts, it is favorable that the powder bed temperature is above T_c , because premature and fast crystallization of the polymer can induce warping and curling. For semicrystalline materials, it is best practice to keep the powder bed temperature within the sintering window, above $T_c(\text{onset})$. Not all materials have a (wide) sintering window, and a more precise set of process parameters is needed to achieve high printability. DSC is one of the most useful tools to identify starting parameters for SLS. As DSC is performed at constant heating and cooling rates, it does not realistically mimic the complex printing

process. The identified parameters have to be treated as starting point from which they need to be optimized further. A benefit of SLS over fused deposition modeling, another commonly employed additive manufacturing technology, is the potential for higher drug loading. Fused deposition modeling formulations usually contain <30% of drug as the necessary intermediate products, the filaments, may become too brittle or too soft. SLS does not have this problem, and it has been demonstrated that is possible to print a dosage form without a polymeric binder and a drug loading of 95% (Kulinowski et al. 2021).

5.2 *Laser Absorptance*

To effectively sinter particles, it is important that the laser light is absorbed by the powder blend and converted to thermal energy. As discussed before, there are two different laser types commonly used for the printing of pharmaceuticals, namely CO₂ lasers and diode laser. The laser light of CO₂ lasers with a wavelength $\lambda = 10.6 \mu\text{m}$ is readily absorbed by most organic materials in the fingerprint region of organic molecules. This increases the conversion efficiency from radiation to thermal energy as the complete or at least most of the formulation will absorb the laser energy.

Diode lasers emit light in the visible spectrum, which is not absorbed by most pharmaceutical excipients and drug substance. To overcome the lack of absorptance of the other formulation constituents, absorbents, e.g., pigments, are added. In industrial applications, carbon powder is often used as an absorbent giving printed parts a characteristic black appearance.

5.3 *Flowability and Spreadability*

Suitable powder flowability is of key importance for robust processing. Powder flow is a complex property that is not easily understood and measured. A multitude of different parameters exist to describe flowability, for example, Carr's index, Hausner ratio, angle of repose, or flow function coefficient (FFC) (Prescott and Barnum 2000). With SLS, flowability is important, but the powder spreading behavior is paramount. Powder spreading can be defined as the formation of thin, dense, and homogeneous powder layers with a powder recoater. Powder spreadability is a specific form of powder flow and equally challenging to assess. Powder spreadability can be improved by the addition of glidants, e.g., fumed silica, talc, and magnesium stearate, by an increase in particle size and a change in particle shape to higher sphericity. While good flowing powder is frequently also well spreadable, the terms cannot be used synonymously. Good flowing powder might have a very low bulk density or high aeration, which would not necessarily result in good spreadability. Nevertheless, common devices to assess powder flow can also be used to obtain basic information on spreadability. The rank order of flowability is

also mimicked in spreadability, but the process dynamics, e.g., different recoating speed or different rotations per minute of a rotating recoater, cannot be captured (Mehrabani et al. 2023).

5.4 Particle Size and Morphology

Particle size and morphology are also important for SLS, as they have a significant influence on the flowability and packing density of the powder. The smaller the particle size, the higher the powder bed density, surface quality, and print accuracy. When particles are very small, they start to agglomerate as van der Waals, electrostatic, and capillary forces begin to dominate the gravitational force. Larger particles become problematic when they approach the set layer height (see Sect. 4.2.1). The particle size most used for industrial application is a median size of 45–90 μm (Goodridge and Ziegelmeier 2017). To ensure high repeatability, it is desirable to have a narrow particle size distribution. With a narrow particle size distribution, the laser melts the polymer more uniformly as the particle surface areas irradiated by the laser are similar. Many pharmaceutical excipients have median particle sizes $>100\ \mu\text{m}$ and comparably broad particle size distributions. A benefit of wider particle size distributions is that small particles can fill the cavities between larger particles and lead to a denser powder packing, which can be used to obtain stronger dosage forms or dosage forms with higher drug loading. However, materials with broad particle size distributions show typically decreased flowability, and it may be useful to process sieve fractions.

5.5 Polymer Aging and Powder Recycling

A large portion of powder in the SLS process remains unsintered and this powder is usually recycled for consecutive prints to prevent material waste. This means that a fraction of the powder is continuously exposed to elevated temperatures for long periods of time. This repeated and prolonged heating of powder can cause a variety of problems, e.g., thermal degradation, a change in particle size and shape due to particle agglomeration caused by sintering, reorientation of polymer chains (enthalpy relaxation), and an increase in molecular weight due to post-condensation reactions and crosslinking leading to a higher melt viscosity (Wudy and Drummer 2019). The closer the powder bed temperature is to the melting temperature of the thermoplastic binder, the faster powder aging takes place. Slight changes in powder behavior can be detrimental to the printing process and can cause prints to fail. To counter the effect of powder aging, the aged powder is generally blended with fresh, so-called virgin powder before it is reused. Recycling of printing powder is essential for the application of SLS in personalized medicine. Personalized medicine is characterized by on-demand manufacturing of small batches. When small batches

are printed, a high amount of unprinted powder will remain, and recycling is a necessity. Although there has been a lot of research on the recycling of polymers in industrial applications, this is not the case for the pharmaceutical application, and more research is needed. As polymer aging is severely accelerated by elevated temperatures, application of a CO₂ laser-based SLS printer with lower processing temperatures might circumvent or reduce this issue.

5.6 *Other Excipients*

While the drug substance and binder likely constitute to the majority of the formulation and dominate the printing behavior, further excipients will also have an influence on powder flowability and spreadability and required process settings. This has to be considered every time an additional excipient is included. These additional excipients are included to modify the properties of the final dosage forms. For example, they may be used to modify dissolution, influence disintegration behavior, or to make dosage forms more appealing. Generally, all excipients that withstand the temperatures during SLS and do not hinder flowability and spreadability significantly can be utilized.

6 **Pharmaceutical Research of SLS**

Despite its widespread application in other industries, SLS only shifted into focus of pharmaceutical researchers around 2017. The first pharmaceutical studies utilizing SLS date back to 2001 (Low et al. 2001), but only a handful of studies have been conducted between then and 2017. Since 2017, more and more studies were published investigating the pharmaceutical application of SLS. The reason for the sudden interest in SLS is the expiration of a patent held by Carl Deckard in 2014, which protected the fundamental process principle (Deckard 1986). All publications before 2017 rely on self-constructed printers, which presented a significant entry hurdle. After patent expiration, multiple companies developed more affordable SLS printers and opened the field up for research.

Pharmaceutical applications deviate significantly from use cases in other industries. In industrial environments where SLS is used for rapid prototyping or low volume, specialty production, it is possible that SLS equipment might not process more than one or two different materials in its lifetime. This means that process parameters and material attributes can be optimized until robust, high-quality printing is achieved (almost) every time. From a pharmaceutical perspective, such an approach is impractical. Drug substances have vastly different physicochemical properties and formulations have to be tailored to accommodate this diversity while also satisfying biopharmaceutical considerations, such as dissolution kinetics or gastro-resistant properties. This high material variability is accompanied by the

frequent lack of different particle morphologies. While some excipients are available in multiple morphologies with different properties, e.g., lactose, the most relevant pharmaceutical excipients, i.e., polymers, are usually only available in one or two different qualities. Therefore, the process must be tailored to allow printing with the limitations imposed by the materials.

A common and frequently applied systematic approach to investigate the influence of process and material on critical quality attributes of dosage forms is *design of experiment*. Design of experiments entails approaches of applied statistics to guide the design, conduction, analysis, and interpretation of controlled experiments. This approach was utilized by Barak Ali et al. to quantify the influence of printing chamber temperature and laser scanning speed on dosage form weight, hardness, disintegration time, and drug dissolution (Barakh Ali et al. 2019). Their findings confirm the principles described above. The higher the energy input in the system, either by increased printing chamber temperature or reduced laser scanning speed, the more bonds are formed between particles and the denser the objects. This resulted in dosage forms of higher mass as especially the increased chamber temperature leads to additional sintering and dosage form growth. The formation of more bonds and denser dosage forms also increased tablet hardness and disintegration time and slowed drug release. The increase in disintegration time and reduction of drug release was explained by decreased porosity and increased density of dosage forms printed with higher energy input.

A major issue in pharmaceutical research is poorly soluble drugs. It is estimated that up to 90% of drugs in the development pipelines are poorly soluble and require some form of enabling formulation to increase bioavailability (Ting et al. 2018). To implement and anchor a novel manufacturing technology, it has to be capable of processing most materials and, therefore, has to be capable of processing poorly soluble drugs. Poor drug solubility is mainly caused by two different factors: high lattice energy of crystalline drugs and high lipophilicity. The lattice energy must be overcome during dissolution to disrupt the crystal lattice and make an individual drug molecule available for solvation. If the drug molecule is highly lipophilic, solvation is hindered because of limited interaction with the (usually) aqueous solvent. Different strategies to overcome these limitations have been developed (Williams et al. 2013). A powerful approach to increase the solubility and dissolution rate of a crystalline drug is its conversion to the amorphous state and stabilizing it in amorphous solid dispersions (Van de Mooter 2012). During the transition to the amorphous state, the crystal lattice is broken up and consequently does not have to be overcome during dissolution anymore. A downside of this approach is that the amorphous state is metastable and drugs tend to recrystallize with time. To prevent recrystallization, drug molecules can be dissolved in polymer matrices to form amorphous solid dispersions. One of the benefits of SLS is that a targeted, well-controlled, and highly localized energy input is used to fuse the particles. This energy can be used to convert crystalline drugs in the amorphous state and disperse them in the polymeric carrier in a one-step process. Until now, this has been demonstrated for ritonavir in a polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VAc) (Davis Jr. et al. 2021), indomethacin in PVP-VAc (Thakkar et al.

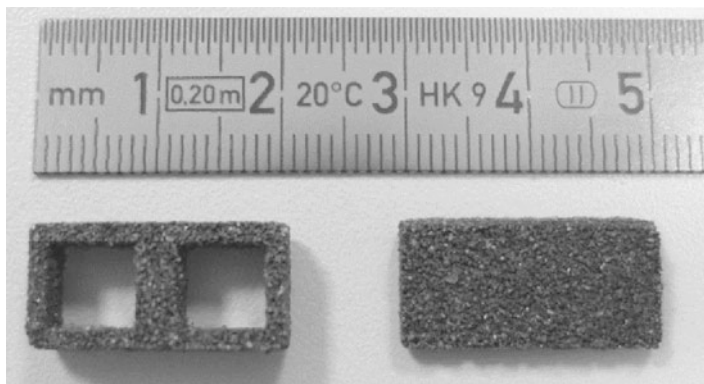


Fig. 11.10 Dosage forms printed from 95% paracetamol and 5% powdered charcoal. (Reprinted from Kulinowski et al. (2021) with permission from Elsevier)

2021), and partial amorphization has been shown for lopinavir in a polyethylene glycol-polyvinyl alcohol graft copolymer (Hamed et al. 2021). In the latter study, a chemometric model was also built to determine the crystalline content based on X-ray diffraction data.

If the drug itself is sufficiently thermoplastic, it is also possible to replace the matrix. A suitable drug substance for this is paracetamol. Kulinowski et al. employed a formulation consisting of 95% paracetamol and 5% powdered charcoal (Kulinowski et al. 2021). Utilizing a 2.3 W diode laser at 445 nm, printing was feasible at different conditions leading to highly drug-loaded dosage forms (Fig. 11.10). The drug remained crystalline, and the dissolution rate could be modified by changing the hatching space. The lowest hatching space, i.e., the print with the highest energy density, was 50 μm and resulted in the slowest drug release with 75% released after 5 h. With a hatching space of 150 μm , 75% of drug were released <1 h.

In all the works mentioned in this section, SLS printers with diode lasers were used. Consequently, colorants, mostly pigments, had to be added to formulations as energy absorbent. Only in a few studies, CO_2 laser-based equipment was employed. A similar influence of powder temperature and laser scanning speed on dosage for weight, hardness, disintegration, and dissolution was found as described by Barakh Ali et al. (Gueche et al. 2021a; Barakh Ali et al. 2019). It has also been possible to fully amorphize up to 20% paracetamol in a PVP-VAc matrix (Gueche et al. 2021c). At present, not enough data is available to demonstrate the superiority of one type of laser source over the other. CO_2 lasers should enable SLS printing at low (er) temperatures compared to diode lasers as polymers can directly absorb radiation emitted from a CO_2 laser. Yet, such a printing approach has not been reported to date.

Little to no research has been conducted specifically on dosage adaption and the modification of release profiles by manipulation of dosage form geometry. The principle that a well-developed formulation and well-developed process will allow

modification of the dosage form dimensions by modification of the dosage form design also holds true for SLS. There is no reason to assume that variations of dosage form size (dosage) are not possible. The resolution of the printed forms is dictated by the particle size of the powder mixture, the laser spot size, and the accuracy of the laser scanning system. It is therefore likely that lower geometric limits for medicines exist depending on powder and equipment. Dosage forms above this critical lower size should be realizable without issues. Similar limitations exist for all other additive manufacturing technologies as well. The influence of dosage form design on dissolution properties has not been covered in systematic examinations, but it should be possible to apply mathematical models developed for other additive manufacturing technologies to SLS.

7 Conclusion

Not all 3D printing technologies are equally suitable for specific use cases. Certain technologies, especially fused deposition modeling and semisolid extrusion, may be applied in distributed settings, e.g., hospital and community pharmacies. They have small footprints, intermediate material can be prepared on-site or industrially, and printing for smaller patient numbers is feasible. SLS contrasts these technologies and has to be considered an industrial manufacturing platform. Equipment costs and processing with drug substances in powder form impose economic and work safety-related issues that will be difficult to solve in decentralized settings. As the technology has been scaled up for other industrial applications, it is a promising candidate to realize mass customization of medicines. Even more so because it has the potential to process poorly soluble drugs, which is more challenging with other technologies suitable for large volume manufacturing.

In this chapter, we have given an introduction to the SLS technology. We have described the fundamentals of the printing process and the different fusion mechanisms and covered the influence of process parameters on quality attributes of dosage forms. We have further introduced the required material properties and presented results from current pharmaceutical research. In the end, the main benefits of SLS lie in its fundamental simplicity combined with its manufacturing and processing potential. In a best-case scenario, only a powder blender is necessary beside the SLS equipment, and no further preprocessing is necessary. This is in contrast to other 3D printing technologies, where filaments have to be produced (fused deposition modeling) or a second formulation has to be developed and prepared (binder jetting). Before SLS can be used for manufacturing of medicines, additional developments are necessary. While commercial SLS machines satisfy highest safety standards as byproducts of industrial SLS can be toxic or explosive, SLS printers do not adhere to cGMP regulations. This, in the end, is a limitation that can be remedied. The process capabilities are vast, and SLS will likely play a role in personalized therapies of the future.

Questions

1. What printing defects can occur when the energy density is excessive?
 - (a) Warping and curling.
 - (b) Poor bonding.
 - (c) Balling.
 - (d) High object porosity.
 - (e) All of the above.
2. What are unwanted effects of powder aging?
 - (a) The molecular weight of polymers will decrease.
 - (b) Thermoplastic polymers will show better flowability and spreadability.
 - (c) The particle size distribution will shift toward larger particles.
 - (d) The main fusion mechanism will change.
 - (e) The melt viscosity can increase.
3. Is it necessary to include support structures when printing an object with an 85° overhang?
 - (a) No, in SLS, the unsintered powder acts as support structure.
 - (b) Yes, similar to fused deposition modeling, support structures are required.
 - (c) No, support structures are not necessary because the printed object is sturdy enough.
 - (d) Yes, support structures are strictly necessary because powder aging may influence the integrity of the printed object.
4. Why is it necessary to add a colorant/absorbent to a formulation when printing with a blue diode laser?

Answer: Light from blue diodes ($\lambda = 445\text{--}450\text{ nm}$) is absorbed in the visible spectrum. Because most pharmaceutical excipients and drug substances are colorless, they cannot absorb laser energy of this wavelength. The light absorptance of the formulation can be increased by adding an absorbent.
5. Why is it common practice to set the powder bed temperature within the sintering window of a semicrystalline polymer?

Answer: To prevent unwanted melting of the semicrystalline polymer, the powder bed temperature is set below the melting temperature T_m of the polymer. Additionally, it is favorable for the powder bed temperature to be above the crystallization temperature T_c , because premature and fast crystallization of the polymer can induce warping and curling.
6. Liquid phase sintering is one of the most important fusion mechanisms in SLS. Which statements about liquid phase sintering are correct?
 - (a) Particles are always completely melted.
 - (b) Liquid phase sintering can be observed in binary mixtures.

- (c) Liquid phase sintering is independent of the energy density.
 - (d) Chemical reactions should not occur.
 - (e) Liquid phase sintering only takes place when a CO₂ laser is used.
7. What are process capabilities of SLS relevant for pharmaceutical application?
- (a) Highly lipophilic drugs can be processed to amorphous solid dispersions to improve drug dissolution.
 - (b) SLS is best suited to process materials with broad particle size distributions.
 - (c) The process can be tailored to accommodate a variety of different materials.
 - (d) Most pharmaceutical excipients can be utilized for SLS.
 - (e) Powder flowability is not limiting for the printing process.
8. Which statements about SLS printing equipment are correct?
- (a) SLS printers can be equipped with different laser sources.
 - (b) It is best to directly measure and control the powder surface temperature.
 - (c) The hatch spacing can be adjusted to modify dosage form properties.
 - (d) The wavelength of a CO₂ laser is 10.6 μm .
 - (e) The process has to be adjusted to accommodate materials of different particle sizes.

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Chapter 12

Bioprinting in Personalized Medications



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Abstract Technology advancements are being sparked by a rising desire for controlled assembly of physiologically relevant materials with predetermined three-dimensional hierarchical structures, with the eventual objective of recreating multicellular tissues and organs to cater to an individual patient's needs. The domain of personalized medicine represents an era of health care in which medicines, devices, and diagnostic or therapeutic procedures could be customized as per the patient's needs, wherein 3D bioprinting is expected to play a major role. This chapter discusses the various techniques of bioprinting as well as the most popular bioinks currently in use. Further, an insight into some of the most influential works in the field of 3D bioprinting for personalized medicine along with the regulatory challenges faced by 3D bioprinted products have been mentioned.

Keywords Bioprinting · Bioink · Personalized medicine · Scaffold

1 Introduction

With an increase in the need for living tissues and organs for a wide-ranging plethora of biomedical applications, the demand for the advancement of tissue engineering that seeks to create functional tissues has escalated (Zhang et al. 2018). The concept

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of three-dimensional (3D) printing was initially patented by Hull in 1986. Since then, various 3D printing methods were developed. Later on, the idea of the inclusion of cells into 3D printed constructs arose that led to the development of 3D bioprinting (Ashammakhi et al. 2018).

Bioprinting denotes the production of scaffolds with the utilization of additive manufacturing (AM) that employs layer-by-layer deposition of bioink having predefined 3D structures that are developed using a computer-aided design (CAD) software. After the selection of an appropriate biomaterial, cell type, and several growth and differentiation factors, a functional and relevant complex 3D tissue and organ could be printed for various uses, including drug screening, drug and biomolecule delivery, disease modelling, and regenerative and personalized medicine (Singh et al. 2020) (Fig. 12.1).

The current methods of bioprinting are essentially one amongst extrusion-based bioprinting, droplet-based bioprinting, or laser-based bioprinting (Datta et al. 2018). Extrusion-based bioprinting uses mechanical, pneumatic or solenoid dispenser mechanisms for the deposition of bioinks in a continual form of filaments, whereas droplet-based bioprinting depends on the formation of bioink droplets through thermal, acoustic, or electrical stimulation (Dey and Ozbolat 2020). In laser-based bioprinting, a laser is used to print 3D structures like in stereolithography by a photopolymerization principle (Zhang et al. 2017).

The introduction of 3D bioprinting has brought the pharmaceutical sector closer to the domain of personalized medicine. Upon administration of the same dose, there could be changes in the medication response between different individuals. The advent of personalized medicine may produce a decreased risk of the adverse effects or the subtherapeutic benefits owing to the dosages lying beyond the therapeutic window, which might result in an improved adherence and better satisfaction for the patients. Personalized medicine comprises suitable dosage forms for special patients, including paediatric, geriatric, or dysphagic population that enables them to use the

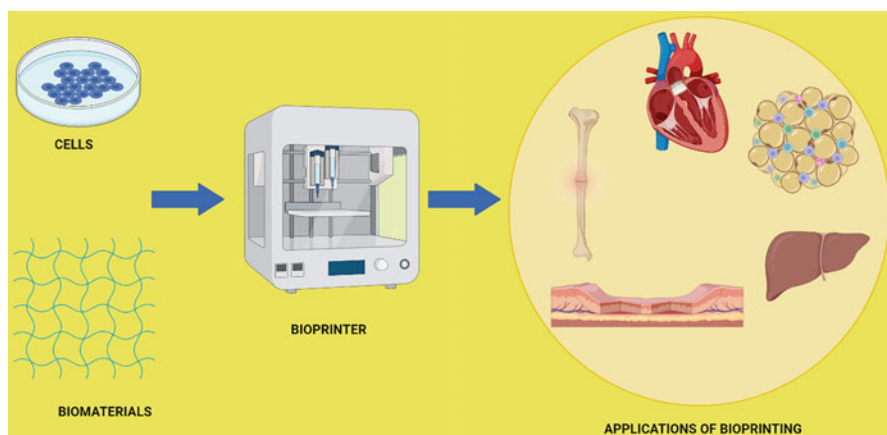


Fig. 12.1 Process of bioprinting and its applications in personalized medicine

preparation. Although the products available commercially could be modified by crushing/breaking tablets or by the opening of capsules, there is always the concern of incorrect doses or inability of the patient to perform certain alterations on a regular basis. The conventional techniques of manufacturing do not offer personalized patient dosing since it is not cost-effective as well as unfeasible. However, on the other hand, 3D bioprinting has a high accuracy as well as an extremely malleable nature and therefore can be used as an alternative manufacturing tool (Chen et al. 2020). Also, 3D bioprinting has enabled biocompatible materials and cells to be deposited in certain locations in three-dimensional space, thereby allowing scientists to avoid the disadvantages of 2D cell culture and invent newer therapies (Morrison and Tomlinson 2021).

The domain of personalized medicine represents an era of health care in which medicines, devices, and diagnostic or therapeutic techniques could be customized as per the patient's needs. 3D bioprinting is anticipated to contribute majorly in the area of personalized medicine. Medicated tablets have been fabricated with the use of 3D printers and have shown to be very efficacious in the customization of drug dosage and the optimization of release profiles (Youssef et al. 2015). Additionally, the 3D printing of a person's unique tissues might enable a future scenario in which a medicine is tested against the person's tissues before being administered in an effort to determine its benefits and potential toxicities (Youssef et al. 2015).

Clinical staff will be able to give treatment that is unique to the patient's size, form, and demands, thanks to the development of personalized medical and surgical equipment. A theoretically infinite variety of intricate and adaptable items, such as prosthesis and surgical tools, may be produced by employing 3D printing techniques and utilized to deliver individualized therapy (Youssef et al. 2015).

3D printing technology has found application in the on-demand fabrication of dosage forms which have been personalized for individual patients, with tailor-made doses, drug combinations, shapes, sizes, and drug-release profiles (Awad et al. 2021). The adoption of 3D bioprinting could pave a way for a personalized healthcare system, by advancement from traditional treatment to digital healthcare and restructuring a new cyber era (Xu et al. 2021).

Till date, a huge majority of the therapies were designed and supplied to an 'average patient' without taking into account the vast diversity existing amongst people. In recent times, personalized medicine is soon evolving as novel methodology in the areas of prophylactic treatment and therapy, by considering the exclusivity in genes of human subjects and lifestyles thereby permitting personalized regimens. This method will play a major part in the near future, for numerous pathological disorders in pre-clinical screening and clinical therapy (Arrigoni et al. 2017).

2 Techniques of Bioprinting

2.1 Extrusion-Based Bioprinting

Extrusion-based bioprinting denotes the main method for the manufacture of comparatively huge tissue constructs that possess a high density of cells. It is based on a working principle that is analogous to that of polymer-based fused deposition modelling rapid prototyping process, wherein the input material undergoes extrusion through a nozzle and the melted polymer will be moulded to its preferred shape in a layer-by-layer manner.

The extrusion-based systems are classified as piston, pneumatic or screw-driven. The screw-driven system is used to extrude materials with a high viscosity material of up to 10^4 Pa.s and is mostly utilized to print thermoplastic polymers such as polycaprolactone. The cell-laden hydrogel could be cast inside the printed thermoplastic structure or be co-printed in a multitechnology production method to form structures having a greater mechanical stability. To print materials having lesser viscosities ($<10^7$ mPa.s), piston- or pneumatic-based extrusion systems are generally employed rather than the screw-driven extrusion system.

The resolution of printing of the deposited structures is chiefly determined by the ink and the diameter of the nozzle. With the use of bioinks, the resolution is often restricted and varies from 100 micrometres to millimetres, since the shear stress that is present at the tip of the dispenser that is inversely correlated to the diameter of the nozzle could be reduced to avoid disruption of the implanted cells. On the contrary, the resolutions achieved with bioinks are much greater since they aren't restricted due to such limitations and can undergo extrusion through thinner microneedles with greater pressures (Schwab et al. 2020).

The advantages of extrusion bioprinting include its capability in printing viscous bioinks (30×10^7 mPa s) that have a greater cell density, and also spheroids into 3D scaffolds. However, the disadvantage linked to this method is its poor resolution (200–1000 μm), possible obstruction of the nozzle and the decrease in the cell viability owing to shear stress (Holzl et al. 2016).

Depending on the design, the software can govern the positions on the build platform on which the bioink should be extruded onto so as to produce the preferred 3D construction. The extrusion is conducted by cylindrical deposition of the substance, by using pneumatic, mechanical, or solenoid driven. The selection of the deposition system is dependent on the sensitivity of the bioink, by progressively pushing it lower without injuring the cell-laden ink. In comparison to the remaining methods of bioprinting, it has a higher speed of printing, and a wide variety of bioinks can be utilized, which include scaffold-free inks or scaffold-based inks. Moreover, it offers enhanced structural rigidity owing to the continual deposition of filaments and easy incorporation with CAD software (Leberfinger et al. 2019).

2.2 Inkjet-Based Bioprinting

In the inkjet-based method of bioprinting, living cells are deposited as droplets via cartridges as an alternative of seeding them on scaffolds. This technique makes use of a noncontact reprographic method which uses digital data obtained from a computer that represents tissue or organs and replicates it onto a substrate with bioink. This process permits printing of single cells or cell aggregates by control of operational factors like concentration of cells, volume of the drop, resolution, diameter of the nozzle, and mean diameter of the printed cells (Ozbolat and Yu 2013).

In inkjet bioprinting, the droplets are produced by two techniques, i.e. thermal or piezoelectric actuation that can undergo ejection through the head of the inkjet nozzle and onto the print substrate. In the thermal actuation method, the heating element can cause superheating of the bioink which creates vapour bubbles to eject the droplets. Though the temperature touches 200–300 °C, the process continues just for a few microseconds that results in an increase in the temperature of ~10 °C in the printer head. However, this elevation in temperature produces negligible destruction to viability of the printed cells (Cui et al. 2017).

In the piezoelectric method, a voltage is induced that causes a rapid change in the shape of the piezoelectric substance. It provides a wide range of inks as compared to the thermal inkjets since there is no need for a volatile constituent, nor any issues of coagulation (Cui et al. 2017).

The remaining inkjet printers make use of an acoustic radiating force, which is linked to an ultrasound field for the ejection of liquid drops from an air-liquid interface. The ultrasound factors which include pulses, time, and amplitude could be modified so as to govern the size of the droplets and the ejection rate. The advantage of acoustic inkjet printers includes their ability of generating and controlling a drop of uniform size and the rate of ejection. Moreover, the shear stress levied on the cells at the nozzle tip wall can be evaded with the use of an open-pool nozzle-free method of ejection. This could reduce the possible harm of cell viability and function as well as avoid the problem of nozzle clogging (Murphy and Atala 2014).

In the inkjet printers available in the market, a majority of the inks should have a reduced viscosity or certain electromagnetic characteristics, which limits the use of inkjet bioprinting. Although inkjet bioprinting has the ability to print several bioinks, the direct inkjet bioprinting of self-supportive tissue constructs still remains a challenge. Also, a lack in the availability of commercial inkjet bioprinters has restricted the promotion of this method (Ji and Guvendiren 2021).

In a study conducted by Nishiyama and co-workers, a custom-made inkjet printer was used to construct various hydrogel structures. An alginate hydrogel was produced by reacting the solutions of sodium alginate and calcium chloride. A sodium alginate solution was ejected from the inkjet nozzle and was further combined with a substrate comprising of calcium chloride solution to construct the gel structure. Additionally, in this 3D bioprinter, the nozzle could be twisted in three dimensions. Thus the advancement of this 3D bioprinter is established by employing living cells

as a material, a novel manufacturing technique that could enable accurate fixation of 3D gel structures (Nishiyama et al. 2009).

The inkjet method of bioprinting includes many advantages such as high-throughput capability, increased resolution, cost-effective, reproducibility and ease in handling (Pati et al. 2016).

2.3 *Laser-Assisted Bioprinting*

Laser-assisted bioprinting (LAB) makes use of a laser pulse in order to create a bubble, wherein the shock waves formed due to the bubble formation ultimately force the cells to transfer toward the collector substrate (Dababneh and Ozbolat 2014) (Li et al. 2016). Although LAB has been renowned for its exceptional resolution, it has been connected with a decreased throughput and is much slower as compared to the inkjet and extrusion methods. To bioprint mesenchymal stem cell grafts, laser-induced forward transfer can help in preserving structure of the graft (Ashammakhi et al. 2018).

Laser-based printing is centred upon the transfer of bioink from a donor substrate to a receiving substrate that is positioned below. This transfer is governed by the pulses of a laser beam which precisely targets a defined position on the energy absorbing layer titanium or gold, which is layered onto the donor substrate. Depending on the amount of energy that is absorbed, droplets of the bioink that are defined in size are produced. This technique permits the printing of materials having a high viscosity and high cell densities at a high resolution, which is however restricted due to the high costs and lack of suitability in the printing of large constructs (Wlodarczyk-Biegun and Campo 2017).

Laser-assisted bioprinting comprises three components, i.e. a donor slide, a laser pulse, and a receiving slide. A ribbon is formed of a layer of transparent glass, a thin layer of metal, and a layer of bioink. When the metal layer that is under the hydrogel is vaporized by a laser pulse, the bioink is shifted from the ribbon onto the receiving slide. This method has higher cell viabilities (>95) as well as a resolution ranging from 10 to 50 μm (Kacarevic et al. 2018).

Keriquel and co-workers revealed that laser-assisted bioprinting could be employed for the in situ printing of mesenchymal stromal cells that is related to collagen and nano-hydroxyapatite, so as to promote regeneration of the bone, in a calvaria defect model in mice. After trying various cell printing orientations, they proved that various cellular geometries have an influence on the regeneration of bone tissue (Keriquel et al. 2017).

Recently, the laser-induced forward transfer (LIFT) has also been demonstrated to be appropriate for bioprinting. This method involves coating of an ink solution on a glass slide followed by coating with a metal or metal oxide so as to absorb the laser. The laser is directed to this metal layer having an ablation spot size that ranges from 40 to 100 μm in diameter thereby producing a local pressure to cause ejection of the ink layer onto the substrate (Ji and Guvendiren 2017).

The laser pulse with high energy has very little influence on the viability of the cell, and also selective writing of multiple cell types is probable. This technique has the ability to position small droplets of the biomaterial at a high resolution. Moreover, high cell densities and hydrogel precursors with any preferred viscosity can be printed. Without a nozzle, this technique has the capability to have accurate control over the deposition of a high-viscosity material (Hong et al. 2018).

The utilization of lasers, specifically with UV light, could leave a detrimental effect on cells. Hence, trials must be performed on the cells or on the receiver tissue for in situ and in vivo bioprinting. LAB also has a fine printing resolution, which means it has a reduced printing speed that isn't suitable in situations that require rapid fabrication due to dehydration (Hong et al. 2018).

2.4 *Stereolithography Bioprinting*

Stereolithography bioprinting utilizes a light to cure a photosensitive resin. This resin usually consists of a photoinitiator and reactive monomers. On exposure to light, the initiation of a reaction takes place which creates a contiguous network. Selective exposure of selected areas of the print area having a suitable wavelength and light intensity enables the building of 3D structures with spatiotemporal control (Choudhury et al. 2018). Stereolithography bioprinting involves two main approaches, i.e. digital light processing (DLP) and two photon polymerizations (TPP).

DLP employs a photomask to cause selective irradiation of the resin. DLP represents a layer-by-layer method of bioprinting. However it is largely suitable to print bigger constructs since it is easy to scale the stage and resin bath. With DLP, a minimum resolution of $\sim 30\ \mu\text{m}$ can be achieved.

However, TPP utilizes an ultrashort near-infrared pulse for curing of the resin with the use of two photon absorbing initiators wherein the light intensity is just sufficient for initiation of a reaction at the focal point of the laser. This method enables printing freely in three-dimensional space at high resolutions.

The resins used for stereolithography need to have a reduced viscosity so that once after curing of a structure in 3D space, the resin which remains unreacted can flow out from the construct. The use of a resin of high viscosity would result in the unreacted material getting trapped in the interstitial space. To ensure cell viability, the toxicity of reactive materials which includes the photoabsorber and photoinitiator and the wavelength and intensity should be controlled.

The printing resolution is also dependent on the light penetration into the resin. The deeper the penetration of the light within the material, the denser is the voxel (TPP)/layer (DLP). A rise in the light diminution results in a decrease in the penetration distance and light scattering thereby producing a reduction in the voxel/layer size and feature resolution (Morgan et al. 2020).

The selective crosslinking of the bioink by light effects in no shear stress to the cells, which enables the bioprinters to gain a great cell viability (>85%). However, the main disadvantage of this method is the requirement of the liquid to be transparent with a restricted scattering, or else the light cannot pass uniformly through the material which would result in a non-uniform crosslinking. Owing to this prerequisite, the cell densities within the bioink are restricted to approximately 10^8 cell mL^{-1} (Heinrich et al. 2019).

Since stereolithography is dependent on quick photopolymerization, many resins used in stereolithography use reactive groups including acrylates and methacrylates, epoxides or vinyl-ethers. The sensitivity of the photoinitiator could be stabilized using a radical-scavenging photoabsorber to function in tandem to define the z resolution of the system. Thus, to define an ideal stereolithography system, cautious calibration of the type of light and its intensity, the concentration of the material and its reactivity, and sensitivity of the photoinitiator and its concentration should be considered (Bedell et al. 2020).

A major drawback of stereolithography is the use of a UV light source that is detrimental to the biocells and leads to skin cancer. However, visible light stereolithography has been reported as an alternative and is under development in bioprinting by optimization and stabilization of the structures (Vanaei et al. 2021).

2.5 *Magnetic Bioprinting*

Magnetic 3D bioprinting which is established on the principle of magnetic levitation has opened up opportunities for assembling 3D multitype co-cultures in the laboratory. This method entails several advantages such as fine spatial control, endogenous production of extracellular matrix, by negating the need of artificial protein substrates as well as the capacity for printing multiple tissue-like structures swiftly. Predominantly, it is a contactless method which employs two methods to manipulate and assemble the cells into a shaped form. Firstly, in the label-free diamagnetophoretic printing, the cell medium along with a paramagnetic buffer is mixed which will then be exposed to an externally applied magnetic field that causes the formation of cell aggregates. A second approach involves the incubation of the cells with a nanoparticle assembly that consists of poly-L-lysine, magnetic iron oxide, and gold nanoparticles to produce a gel through electrostatic interactions. The uptake of gel by the cells results in them becoming magnetic, which enables them to be manipulated and allowing the cells to drift off the surface of the plate and onto a media wherein cell aggregates are formed. The cell aggregates that are magnetized are arranged into a 3D pattern by a mild magnetic field produced by a pre-manufactured magnetic pattern. By modifying the geometry of the magnetic template that is utilized, spatial modelling of the cell aggregates could be varied (Matai et al. 2020).

Souza and co-workers for the first time proposed and assessed an in vitro 3D model to evaluate human uterine contractility. The application of 3D magnetic bioprinting is to outline the human myometrium cells in the form of rings, so as to

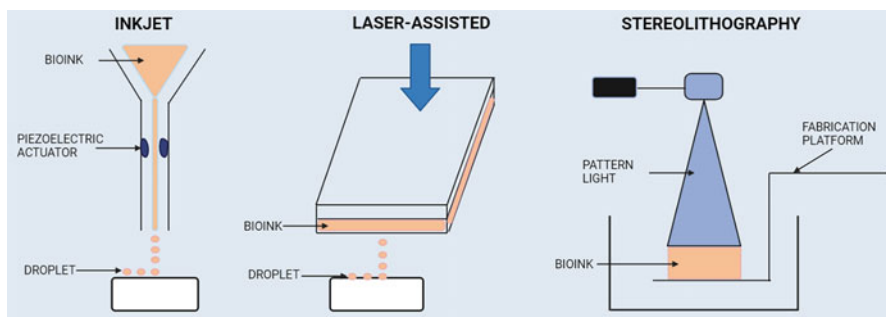


Fig. 12.2 Techniques of bioprinting

monitor contractility over a period of time. The commercial and the patient-derived myometrium cells were bioprinted into rings in a 384-well format magnetically for throughput uterus contraction examination. It was observed that the uterine rings derived from different cell origins and patients exhibited varied forms of contraction and react in a different manner to uterus contraction inhibitors, i.e. indomethacin and nifedipine. Thus, this method could potentially function as a beneficial technique to determine the physiology of human parturition together with allowing an increased-throughput analysis of numerous agents and conditions (Souza et al. 2017). Figure 12.2 represents the different techniques of bioprinting.

2.5.1 Bioinks

The process of biofabrication engulfs a wide range of manufacturing methods that includes bioprinting, wherein cells, biomaterials, and biologically active factors are printed into 3D constructs. Thus, a prerequisite for bioprinting is a ‘bioink’ that could be described as ‘a formulation of cells appropriate for processing by an automated biofabrication technique which could also comprise biologically active constituents and biomaterials.’

The design and use of bioinks have broadened vastly in the past few years that now encompass several materials, i.e. primarily natural and synthetic hydrogels that are applied or developed to fulfil the rigorous demands of bioprinting. The materials have to undergo a conversion from the liquid to solid phases at the proper stage, whether they are processed by extrusion bioprinting or lithography bioprinting. The rheological characteristics of the bioink are vital to the accomplishment of the bioprinting method, and the bioink and processing stages should encapsulate and maintain the viable cells.

Though noteworthy development has been made with respect to the engineering of bioinks for bioprinting, further advancement in this domain will enhance the encapsulation of the cells in a microenvironment which simulates the intricacy of the native tissues and organs, especially by incorporating newer signals and further

processing at an amplified resolution (Sun et al. 2020a, b). Several types of bioinks have been discussed in the further sections. A summary of the naturally derived bioinks and synthetic bioinks have been mentioned in Tables 12.1 and 12.2, respectively.

Table 12.1 Nature-derived bioinks used in bioprinting

Biomaterial	Cell type	Printing method	Outcomes	References
Alginate	Cartilage	Extrusion	Higher expression of cartilage-specific genes in alginate hollow filament encapsulating CPCs	Zhang et al. (2013)
Collagen	MSCs	Extrusion	Osteogenic differentiation was achieved in anisotropic soft collagen-rich substrate	Duarte Campos et al. (2015)
Silk	hTSMCs	Multi-head deposition system	Higher levels of chondrogenic/adipogenic and osteogenic differentiation in the silk fibroin-gelatin blends of tissue constructs	Das et al. (2015)
Gelatin	MSC	Extrusion	Alginate and agarose bioinks supported development of hyaline-like cartilage tissues. High level of MSC viability (~80%)	Daly et al. (2016)
Hyaluronic acid	Chondrocytes and osteoblasts	Extrusion-based	HA-based matrixes were better for cartilage tissue engineering Survival and function of cells within 3D bioprinted structures were maintained up to 14 days in vitro	Park et al. (2014)
Fibrin	Chondrocytes from rabbit ear cartilage	Inkjet	Chondrocytes survived within the printed hybrid construct with >80% viability Printed hybrid scaffolds demonstrated enhanced mechanical properties compared to printed alginate or fibrin-collagen gels alone	Xu et al. (2012)
dECM	Human adipose tissue-derived mesenchymal stem cells	Dispensing system	Printed decellularized adipose tissue (DAT) constructs expressed adipogenic genes more intensely than did non-printed DAT gel	Pati et al. (2015)
Hydroxyapatite	hMSCs	Inkjet	Cell viability 86% after 21 days	Gao et al. (2014)

Table 12.2 Synthetic bioinks used in bioprinting

Scaffold material	Bioprinting method	Cells	Outcome	References
Pluronic	Extrusion based	Chondrocytes	A high pluronic concentration at the beginning of the printing process created a pluronic-based bioink that had good 14-day cell viability	Muller et al. (2015)
PVP	Inkjet	Neonatal human fore-skin fibroblasts	2.5% w/v PP bio-ink displayed consistent cell output for 30 min	Ng et al. (2017)
Poloxamer 407	Extrusion-based	hMSC	Better understanding of the cell viability rates Not only shear rate but residence time of cells at elevated shear rates needs to be considered for improvement of cell survival	Paxton et al. (2017)
PEG	Extrusion	hMSCs	hMSCs maintained a grid-like pattern after 2 weeks and the cells deposited sufficient matrix leading to a skin-like tissue	Rutz et al. (2015)
PCL	Inkjet	C20A4	Cell viability in the hybrid constructs was high after printing as well as after 1 and 3 days of in vitro culture	Schuurman et al. (2011)
PEG	Inkjet	NIH 3 T3	LIVE/DEAD viability/cytotoxicity-stained cross-sectional images indicated the bioprinted cell structures were viable in culture for 4 weeks	Skardal et al. (2010)
PCL	Inkjet/electrospinning	Rabbit chondrocytes	Cell viability was >80% after 7 days	Xu et al. (2012)

2.5.2 Hydrogels

One of the most regularly utilized materials for bio-inks includes hydrogels that are a hydrated network of crosslinked natural or synthetic polymers. These polymers are usually hydrophilic in nature that permits the gel to swell in a milieu that has high moisture content. The hydrogel constituents have high biocompatibility and are also biodegradable, which is a prerequisite for in vivo uses. Additionally, the cells experience encapsulation in 3D when the hydrogel undergoes gelation. In spite of these advantages, a major drawback of the hydrogels is that they have poor mechanical characteristics. They also do not preserve their designed shape (Donderwinkel et al. 2017).

2.6 Naturally Derived Bioinks

Bioinks that have been derived from animal and plant sources are used for the purpose of bioprinting. As compared to the bioinks derived from plants, the bioinks obtained from animals facilitated a much greater cell growth and function. Moreover, the naturally derived bioinks have a much better capacity in supporting cell viability and growth as compared to the synthetic bioinks.

2.7 Alginate-Based Bioinks

Alginate, which is an anionic polysaccharide of mannuronic acid and glucuronic acid that is derived from seaweeds and algae, produces a tough hydrogel on adding calcium ions owing to sodium-calcium ion exchange reactions. A major drawback with the use of alginate bioinks is that they form soft gels at a low concentration. Researches have attempted crosslinking with calcium ions in order to prevent this. In the crosslinking process, the printed constructs are exposed to calcium chloride solution, which causes the exchange of sodium ions with calcium ions wherein the divalent calcium ions result in the formation of a crosslink between two carboxyl groups of the same or different polymer chains (Panwar and Tan 2016).

2.8 Collagen-Based Bioink

Collagen which is a main constituent of the extracellular matrix is obtained from biomaterials derived naturally and is utilized as a bioink material for 3D bioprinting due to its excellent biocompatible characteristics. The crosslinking of collagen can be performed with temperature or pH modification or by using riboflavin. The crosslinking of collagen results in an increase in the tensile strength and visco-elastic characteristics as compared to the non-cross-linked collagen. Nevertheless, the process of crosslinking collagen requires at least 30 min for the formation of a gel at a temperature of 37 °C. Thus, the use of collagen as such in 3D printing is tedious. Nevertheless, its combination with various gelation materials can overcome this difficulty (Gopinathan and Noh 2018).

2.9 Fibrin-Based Bioinks

The protein fibrin is produced when fibrinogen and thrombin are mixed. It also undergoes easy crosslinking by incubating it with fibrinogen, calcium ions, and thrombin. For its use in 3D bioprinting, its characteristics could be modified by

changing the fraction of its constituents that renders it useful as a bioink to be used in 3D bioprinting.

Fibrinogen in the pure form leads to the formation of a hydrogel that possesses poor viscosity and hence is generally printed by inkjet bioprinting techniques. In extrusion bioprinting, it is utilized in combination alongside other biomaterials since it has an exceptional bioactivity and mechanical strength after it is crosslinked. When fibrin is blended with gelatin, alginate and collagen, it provides a bioactive cue as well as sufficient mechanical properties to the bioprinted constructs for improved shape integrity. A main drawback with the use of fibrin is its rapid and irreversible formation of a gel at body temperature, thus making its bioprinting a tedious task. This can be overcome by printing the thrombin and fibrinogen blends together at a low temperature so as to avoid the premature crosslinking. The deposition of thrombin could also be done separately on the construct for crosslinking following the bioprinting of the 3D construct (Murphy et al. 2013).

2.10 Hyaluronic Acid

Hyaluronic acid (HA) that is a constituent of the extracellular matrix comprises a glycosaminoglycan biopolymer which consists of disaccharide unit repeats of D-glucuronic acid and N-acetyl-D-glucosamine.

The hyaluronic acid hydrogel possesses a high viscosity for the purpose of bioprinting. The high viscosity contributes to its use as a supportive hydrogel to adjust the viscosity of the bioinks.

Though HA possesses a high viscosity, the constructs embedded with cells are unable to grasp the 3D bioprinted structure owing to its weak mechanical properties, which results in poor shape fidelity. This problem was overcome by crosslinking hyaluronic acid by a physical and photochemical method. The incubation of HA bioinks were carried out at room temperature when they physically crosslinked, while in photochemical crosslinking, HA modification is performed along with methacrylate. Although a tremendous biopolymer due to its viscosity, HA does present a stability problem wherein it suffers from the problem of rapid hydrolysis owing to its hydrophilic nature (Panwar and Tan 2016).

2.11 Decellularized Extracellular Matrix

The advancement of decellularized bioinks has created an opportunity for the sourcing of a native extracellular matrix to the cells. The extraction of decellularized matrix (dECM) is carried out from animal origins for tissue engineering. Since it is obtained from various tissues, it has an abundance of cell growth and differentiation factors that support the development as well as functioning of certain cell lines. In a case where crosslinking does not afford an adequate amount of mechanical strength

to support the cell-laden 3D bioprinted structure, the shape fidelity could be improved with the use of an external support that could include co-printed synthetic scaffold for the purpose of 3D bioprinting of the cell-loaded constructs (Pati et al. 2014). A few challenges of using dECM as a bioink include its low shape fidelity due to its weak mechanical integrity as well as its rapid biodegradation that does not match the rate of new extracellular matrix generation (Wolf et al. 2012).

3 Applications of Bioprinting in Personalized Medicine

3.1 Bone/Cartilage

Cartilage injury often escalates to the problem of dysfunction of the joints. However, the current joint prostheses that exist are not adaptable with the joint tissue of the host. In a study conducted by Sun and co-workers, an anisotropic cartilage that was regenerated by 3D bioprinting and released dual factors was described. The mesenchymal stem cells loaded hydrogels that released the dual factor resulted in anisotropic chondrogenic differentiation, whereas the physical gradient synthetic biodegradable materials imparted mechanical integrity. Moreover, upon evaluating the cartilage tissue in vitro and in vivo displayed a degree of tissue growth and organization that has the potential to be translated to patients (Sun et al. 2020a, b).

Nulty and co-workers demonstrated the versatility of a 3D bioprinting method for the engineering of prevascularized tissues in vitro as well as the ability of these structures to improve the vascular and regeneration of bone defects in vivo. The fibrin-based hydrogel supported the sprouting of the human umbilical vein endothelial cell (HUVEC) together with establishing a microvessel network which was found to persist in vitro as well. The therapeutic use of these bioprinted constructs were assessed by prevascularization of 3D printed polycaprolactone scaffolds that were eventually embedded into femoral bone abnormalities in rats. Microcomputed tomography angiography displayed raised intensities of vascularization in vivo that correlates to greater levels of bone development (Nulty et al. 2021).

In a research conducted by Cui and co-workers, a bioprinting system having simultaneous photopolymerization that had the capability three-dimensional cartilage tissue engineering was developed. Bioprinting of poly(ethylene glycol) dimethacrylate possessing human chondrocytes was performed in order to correct the flaws in osteochondral plugs in a layer-by-layer manner. The human chondrocytes that were printed were found to retain their positions in which they were initially deposited because of concurrent photopolymerization of the surrounding biopolymeric scaffold that is required for accurate distribution of the cell for anatomically engineering the cartilage. The printed cartilage implant was found to attach steadfastly with the neighbouring tissue, and a higher deposit of proteoglycan was noticed at the interface of the implant and native cartilage when stained with Safranin-O. The results indicated that the cartilage that was printed in 3D biopaper possessed increased glycosaminoglycan levels in comparison to that devoid of

biopaper when normalized to DNA. The results highlighted the potential of anatomic cartilage that was engineered with the help of 3D bioprinting techniques (Cui et al. 2012).

Shim and co-workers built a mechanically superior 3D bioprinted construct that contained dual-cell kinds for the purpose of osteochondral tissue regeneration. A multi-head tissue/organ building structure that was specifically intended for dispensing thermoplastic biomaterial and hydrogel that had varied rheological characteristics was employed for bioprinting the osteochondral tissue. The 3D constructs loaded with the two different cells that consisted of osteoblasts and chondrocytes were efficaciously created. Moreover, the osteoblasts and chondrocytes that were dispensed separately didn't just retain their original position and viability but continued to proliferate for 7 days after being dispensed (Shim et al. 2016).

Shim and co-workers demonstrated a 3D printing method to prepare a 3D construct of multi-layers that contained human mesenchymal stromal cells along with a hydrogel comprising of atelocollagen and supramolecular hyaluronic acid. The fabricated structure exhibited an excellent regeneration capacity to reconstruct an osteochondral tissue in the knee joints of rabbits. The mechanical stability of the host-guest chemistry-based hydrogel was necessary to allow a dual variety of extracellular matrix hydrogels to be printed and arranged into a multi-layered construct thereby negating the usage of dangerous chemical substances or physical stimuli for post-crosslinking (Shim et al. 2016).

In the work conducted by Freeman and co-workers, 3D bioprinted implants were fabricated that contained spatiotemporally defined arrays of growth factors. Further, the optimization of these growth factors was carried out in order to couple angiogenesis and osteogenesis. The implants were printed with nanoparticle-functionalized bioinks, wherein the implants had distinctive growth factor patterns and an extended release profile. The printed implants contained a gradient of vascular endothelial growth factor, which was paired with spatially defined BMP-2 localization and release kinetics, and was found to accelerate the healing of large bone defect along with a slight heterotopic bone production. The study demonstrated the immense opportunity in the printing of growth factor that represents a reputed approach of maintenance therapy for tightly controlled tissue regeneration (Freeman et al. 2020).

Articular cartilage injury is one of the most common ailments in congenital joint dysplasia patients. The growth differentiation factor 5 (GDF5) has been identified as a shared gene in joint dysplasia by genetic studies. Sun and co-workers reported a genetic relation between GDF5 loci and hip joint dysplasia by the genome-wide association study (GWAS). Using 3D bioprinting, a GDF5-conjugated bone marrow stem cell-laden scaffold, a functional knee articular cartilage construct was fabricated for the purpose of repairing the cartilage. A GDF5-conjugated scaffold exhibited superior cartilage repairing ability than the control. Transplantation of the bioprinted GDF5-conjugated bone marrow stem cell-loaded scaffold in rabbit knees offered long-lasting chondroprotection (Sun et al. 2019).

3.2 Vascular

In a study conducted by Izadifar, a nano-reinforced hybrid cardiac patch loaded with human coronary artery endothelial cells (HCAECs) was biofabricated that had superior electrical, mechanical and biological behaviour. The hybrid hydrogel constructs that comprised of carbon nanotube integrated alginate structure, and cell-loaded methacrylated collagen was created using a UV-integrated 3D bioprinting method. The highly interconnected nano-fibrous network provided by the functionalized carbon nanotubes was found to significantly improve the viscoelastic behaviour and electric conduction of the photo cross-linked methacrylated collagen. Moreover, the carbon nanotube strengthened 3D-printed hybrid construct possessed considerably greater stiffness and electric conductivity especially in the physiologically significant frequency range of 5 Hz. Also, for a given carbon nanotube mass ratio, the HCAECs displayed substantial cellular proliferation, migration and variation during incubation of a period of 10 days *in vitro* (Izadifar 2018).

In the study undertaken by Szklanny and co-workers, millimetric vessel-like scaffolds and 3D bioprinted vascular tissues were interconnected to create a completely engineered vascular construct for the purpose of implantation. The endothelial and support cells immediately formed microvascular links in bioprinted tissues with a human collagen bioink. A cuffing microsurgery was used, wherein anastomosis of the engineered tissue with the femoral artery of the rat was performed, which promoted an abundant host vascular network in the tissue which was implanted. Subsequently, after a period of 2 weeks *in vivo*, contrast microcomputer tomography imaging and lectin perfusion of the explanted engineered tissue confirmed the host ingrowth vasculature's function. Moreover, the hierarchical vessel system supported the *in vitro* function of the cardiomyocytes. Thus this research presented an innovative method to produce entirely engineered patient-specific dense tissue flaps (Szklanny et al. 2021).

Duan and co-workers employed 3D bioprinting in order to produce a live alginate/gelatin hydrogel valve conduit having anatomical design. The acellular 3D printed hydrogel was found to possess decreased modulus, higher strength and a peak strain diminishing gradually over 7-day culture, whereas the tensile biomechanics of the cell-loaded hydrogels were effectively bioprinted by directly encapsulating the aortic root sinus smooth muscle cells (SMC) in the valve root and aortic valve leaflet interstitial cells (VIC) in the leaflets. The SMC which was encapsulated displayed enhanced the smooth muscle actin, whereas VIC resulted in increased vimentin. This indicated that the anatomically intricate, heterogeneously encapsulated aortic valve hydrogel constructs could be produced using 3D bioprinting (Duan et al. 2013).

Cui and Boland produced micron-sized fibrin channels by employing a drop-on-demand polymerization technique. This method of printing utilized an aqueous process that induces very little to almost negligible damage to cells. When the human microvascular endothelial cells (HMVEC) were printed in conjunction with fibrin, the cells aligned themselves within the channels and proliferated to form

confluent linings after 21 days of culture. The 3D tubular assembly was also observed in the printed configurations which confirmed the functionality of the printed human microvasculature. The fabricated microvasculature also showed some integrity after 14 days (Cui and Boland 2009).

3.3 *Diabetes*

Ahn et al. produced a long-lasting, 3D bioprinted construct for insulin secretion for subcutaneous implantation to treat type 1 diabetes. The construct was developed by using multi-layer bioprinting of beta-cell mouse insulinoma-6 (MIN-6) encapsulated alginate bioink and polycaprolactone biodegradable polymer. A glucose response assay indicated that the constructs which were bioprinted were found to proliferate and release insulin for a 4-week in vitro period. The in vivo studies which were performed on type 1 diabetic mice also displayed a three times greater secretion of insulin and regulated glucose amounts for 8 weeks after the bioprinted construct was implanted (Ahn et al. 2022).

3.4 *Tissue Fabrication*

Merceron and co-workers used the integrated organ printing technique to process and deposit four different constituents in order to fabricate an integrated muscle-tendon construct. For elasticity and muscle development, thermoplastic polyurethane was co-printed with C2C12 cell-loaded hydrogel-based bioink on one side, whereas for stiffness and growth of tendon, poly(ϵ -caprolactone) was co-printed along with NIH/3 T3 cell-laden hydrogel-based bioink on the other side. The aforementioned constructs displayed more than 80% cell viability after 1 and 7 days of printing, together with preliminary tissue growth and differentiation. Thus this work demonstrated the versatile nature of this technology in the formation of integrated tissue constructs possessing location-selective biologic and mechanical features for muscle-tendon unit engineering (Merceron et al. 2015).

The laser-assisted method of bioprinting presents an efficacious technique for patterning cells, biomolecules and biomaterials. Catros and co-workers fabricated a model for microtissue production that combined laser-assisted bioprinting and electrospinning and have also demonstrated cell viability and cell proliferation in vitro and in vivo, respectively. Live-dead assay and scanning electron microscopy indicated that the printed cells were found to survive and were found to spread onto the printing substrate, which was a polycaprolactone electrospun scaffold. The cell amount was found to be elevated in vitro and in vivo when the materials and cells were piled layer by layer as displayed by luciferase tracking. The histology study of the in vivo samples also indicated a denser fibrous tissue in the layer-by-layer samples (Catros et al. 2012).

3.5 Wound Healing

The stem cells derived from amniotic fluid display a great degree of proliferation in culture and multilineage differentiation capability. Skardal and co-workers employed the bioprinting technique for the treatment of full-thickness skin wounds in nu/nu mice. The amniotic fluid-derived stem cells and bone marrow-derived mesenchymal stem cells were resuspended in a gel constituted with fibrin-collagen and printed over the wound area. The histology samples on evaluation revealed an increase in the micro-vessel density as well as the capillary diameters in the stem cells derived from the amniotic fluid in contrast to the mesenchymal stem cell-treated wounds. Thus the bioprinting of amniotic fluid-derived cells represents an effective method to treat extensive wounds and burns (Skardal et al. [2012](#)).

3.6 Neural System Repair

Hsieh and co-workers synthesized two thermo-responsive water-based biodegradable polyurethane dispersions (PU1 and PU2) that form a gel at 37 °C, minus a crosslinker. The neural stem cells (NSCs) were loaded into a polyurethane dispersion prior to gel formation and was further printed and stored at 37 °C. The NSCs exhibited exceptional proliferative capacity and differentiation in 23–30% hydrogels. When inoculated into a zebrafish embryo neural injury model, the NSC-loaded 25–30% PU2 hydrogels were able to revive the functioning of the compromised nervous system. Additionally, the normal functioning of the adult zebrafish having traumatic brain injury was restored when the 3D-printed NSC-loaded 25% PU2 constructs were implanted (Hsieh et al. [2015](#)).

3.7 Drug Screening

In the work conducted by Xie and co-workers, the isolation and mixing of primary hepatocellular carcinoma (HCC) cells with gelatin and sodium alginate were carried out for the formation of the bioink for printing. The patient-derived 3D bio-printed HCC (3DP-HCC) models were developed that possessed the characteristics of the parental HCCs that included a steady expression of the biomarker, a steady maintenance of the genetic modifications and expression outlines. The aforementioned model displayed the data of drug screening instinctively and quantitatively, thereby proving to be dependable in long-term culture as well as possessing the ability to determine patient-specific drugs for personalized therapy (Xie et al. [2021](#)). A summary of the applications of bioprinting in personalized medicine has been listed in Table [12.3](#).

Table 12.3 Applications of bioprinting in personalized medicine

Scaffold material	Bioprinting method	Tissue	Cells	Outcome	References
Alginate, gelatin and hydroxyapatite	Microextrusion	Bone	Human MSCs	High cell viability of 85% after 3 days	Wust et al. (2014)
poly(ethylene glycol) dimethacrylate	Inkjet	Cartilage	Human chondrocytes	Viability of printed human chondrocytes increased 26% in simultaneous polymerization	Cui et al. (2011)
Agarose	Microextrusion	Bone/cartilage	Human MSCs and MG-63 cells	Histological and immune-histochemical analysis after 14 and 21 days revealed viable cells with marked matrix production and signs of proliferation	Duarte Campos et al. (2015)
GelMA	Microextrusion	Bone/cartilage	MSCs	Quantitative RT-PCR results suggested genomic expression patterns leading to simultaneous differentiation of MSCs into osteogenic and chondrogenic phenotype	Gurkan et al. (2014)
Collagen	Microextrusion	Skin	Fibroblasts and keratinocytes	Highly viable proliferation of each cell layer was observed on the planar and non-planar surfaces	Lee et al. (2009)
Fibrin-collagen	Microextrusion	Skin	Amniotic fluid-derived stem cells	Significant wound closure and re-epithelialization by AFS cell- and MSCs at 0, 7 and 14 days	Skardal et al. (2012)
Gelatin	Laser	Skin	Fibroblasts	High post-transfer viability ($91 \pm 3\%$) and no double-strand DNA damage	Schiele et al. (2011)
Collagen	Laser-assisted bioprinting	Skin	Fibroblasts and keratinocytes	Proliferation of keratinocytes was observed in the supra-basal layers	Michael et al. (2013)

4 Regulatory Aspects

In recent times, the advancements in three-dimensional bioprinting processes and products are escalating at an astonishing rate. The regulation of bioprinted products presents a major challenge in the healthcare sector, especially in the pharmaceutical industry. Owing to the high extent of personalization with respect to the shape of the construct and the genetic constituent, the bioprinted material is often referred to as a 'customized device'. Including biological components muddles the scenario, wherein governing agencies over the world like the FDA have failed to remain up to date in the rapidly evolving arena of bioprinting, where there is presently vague management and guidelines for such kind of technologies (Lim et al. 2018). These challenges must therefore be addressed by the concerned regulatory bodies and institutions that are in the pursuit of producing and marketing tissue-engineered products for clinical use (Jovic et al. 2020). The FDA in 2017 drafted a technical guidance regarding the production of prosthetic devices by employing 3D bioprinting. Nevertheless, the technical deliberations and guidelines with respect to 3D bioprinted produces were not dealt with and are anticipated to be released in the near future (Seoane-Viano et al. 2021). The EU regulatory bodies have recognized the trials that are posed due to complexity of these novel products and have realized the need to develop serious supervision with more trials arising. In the UK as well, regulatory bodies like the MHRA need to engage prematurely in the progress of the processes and pathways that would eventually satisfy the criteria needed in order to scale tissue-engineered constructs for clinical trials as well as for commercial production (Jovic et al. 2020).

Another major factor to implement 3D bioprinting in the healthcare industry is the need to standardize 3D printers so as to fulfil the regulatory and quality control necessities, together with the usage of authenticated software in order to regulate the whole procedure.

Additionally, although various 3D printers were utilized for the printing of dosage forms and medical devices during research, those 3D printers weren't initially adopted to produce pharmaceutical products and thus do not fulfil the good manufacturing practice (GMP) guidelines. Till date, only one 3D printer for personalized medicine is commercially available in the market that has been specially designed and validated as per the GMP guidelines. Additionally, there are certain 3D bioprinting technologies which are more suitable for the production of personalized medicines, such as semi-solid extrusion that has the potential to be one of the first techniques to be used in the preparation of medicines, since a vast majority of the excipients are either pharmaceutical, food-grade, or listed as generally recognized as safe (GRAS) (Seoane-Viano et al. 2021).

Multiple Choice Questions (MCQS)

1. Three-dimensional printing technique can also be termed as ...
 - (a) High-definition printing
 - (b) **Additive manufacturing**

- (c) Novel designing technology
 - (d) Biological printing
2. The file format understandable for 3D printer is ...
- (a) Portable document format (PDF)
 - (b) Document format (doc)
 - (c) Excel spreadsheet (XLS)
 - (d) **Standard Tessellation Language (STL)**
3. The most commonly used word in 3D printing is ...
- (a) Software
 - (b) Computers
 - (c) **Prototype**
 - (d) Analysis
4. The adaptable method of printing under 3D method utilizes ...
- (a) **Single nozzle**
 - (b) Double nozzle
 - (c) Ink jet printing
 - (d) Fused nozzle
5. What terminology is used when we need to move an object in 3D structure?
- (a) Push
 - (b) Pull
 - (c) **Translate**
 - (d) Forward
6. Which term below is best suitable exploit for fused deposition modelling (FDM)?
- (a) Difficult method for fabrication
 - (b) Very expensive
 - (c) **Cost-effective**
 - (d) Tough reproducibility
7. What is the major underlying fundamental under 3D printing?
- (a) Subtractive
 - (b) **Additive**
 - (c) Hot melting
 - (d) Condensation and additive
8. The most expensive paradigm of 3D printing technique is ...
- (a) Selective laser sintering (SLS)
 - (b) Fused deposition modelling (FDM)
 - (c) **Selective laser melting (SLM)**
 - (d) Ink-jet printing

9. What form of construction material employed in ink-jet 3D printing?
- (a) Solid form
 - (b) **Liquid form**
 - (c) Semi-solid form
 - (d) Gaseous form
10. Which of the following is not a liquid-based rapid prototyping model?
- (a) Stereolithography Apparatus (SLA)
 - (b) Solid Object Ultraviolet-Laser Printer (SOUP)
 - (c) Solid Ground Curing (SGC)
 - (d) **Laminated Object Manufacturing (LOM)**
11. What is the important base fabricating material incorporated in stereolithography method?
- (a) **Photopolymer**
 - (b) Thermoplastic, metal powders
 - (c) Eutectic metals
 - (d) Insert alloys
12. Which of the following construction material provides a finest surface finish to the model?
- (a) **Polylactic acid (PLA)**
 - (b) Nylon
 - (c) Acrylonitrile butadiene styrene (ABS)
 - (d) Poly ether ester ketone (PEEK)
13. The major domain of the personalized medicines is . . .
- (a) Pharmacokinetics
 - (b) Drug profile
 - (c) Adaptability
 - (d) **Pharmacogenomics**
14. Which of the following is not a type of extrusion-based system?
- (a) Piston
 - (b) Pneumatic
 - (c) **Fluidized**
 - (d) Screw-driven
15. Which of the statements best describes bioprinting?
- (a) Fabricating biological tissues using living cells only using a 3D bioprinter
 - (b) Using living organisms to fabricate non-living tissues
 - (c) **Fabricating biological tissues using living cells and non-living cells only using a 3D bioprinter**
 - (d) Fabricating non-living tissues using a 3D bioprinter

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Chapter 13

Shape Memory Materials and 4D Printing in Pharmaceutics



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Abstract With 4D printing, time is treated as the fourth dimension, allowing printed structures to change their form independently. These products, created from “smart materials,” respond to stimuli such as light, temperature, water, or pH, changing their shape and creating structures that can adapt and respond to their surroundings. Pharmaceutical formulations have yet to utilize this technology since it is so new. Smart materials are, however, already being used in the industry to create bioadhesive devices that respond to pH to target specific parts of the GI tract, as well as remote-controlled “micro-robots” delivering chemotherapy directly to tumor sites. Earlier innovations in smart materials will probably pave the way for 4D printing’s inevitable adoption. This will allow therapeutics to be developed that combine additive manufacturing’s personalization capabilities with “smart materials” intelligent kinetics. This chapter reviews smart materials and 4D printing considering their applications in the pharmaceutical industry.

Keywords Shape memory materials · Additive manufacturing · 4D printing · Pharmaceutics

1 Introduction

Additive manufacturing is the technology of manufacturing 3D objects from a digital model by adding layer upon layer of materials. These materials can be polymers, metals, concrete, and even human tissue. The inherent ability of this technology for making complex 3D objects, the reduction of waste, time, and cost of the manufacturing process, makes it the future of manufacturing methods in various

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industries. Aerospace, automotive, and biomedical industries benefit the most from additive manufacturing. Additive manufacturing can customize and personalize dosage forms, regenerative medicine, prosthesis, implants, tissues, and medical products in biomedical applications. Recently, 3D printing technology has been accepted by the pharmaceutical industry, with the first 3D-printed drug product (Spritam (levetiracetam) developed by Aprelia Pharmaceuticals using their ZipDose technology) approved by the FDA (Food and Drug Administration) in 2015 (Goole and Amighi 2016). Tailoring precise dosage, shapes, and drug release profile is the most essential issue for rational drug therapy. The term “drug delivery” refers to formulations, manufacturing techniques, storage systems, and technologies that transport pharmaceutical compounds to their target sites so they can achieve the desired therapeutic effects. To enhance drug effectiveness and minimize unwanted side effects, innovative delivery systems are required as a replacement for traditional manufacturing methods characterized by quick release. In addition, drug delivery instruments should be designed based on their specific applications to ensure their optimal performance for drug release (Afzali Naniz et al. 2022). In recent years, the concept of drug delivery has developed from immediate-release oral dosage forms to targeted-release drug delivery systems. In fact, the need to control the drug discharge profile to balance the absorption, dispersion, and elimination of the medication quickly became a key factor for moving forward product viability and safety as well as increasing the compliance of patients. Therefore, conventional manufacturing strategies utilized to create immediate-release systems (e.g., direct tableting, capsule filling) dynamically advanced toward multistep fabricating technologies, including granulation, extrusion, or coating processes to permit the improvement of controlled-release systems (Goole and Amighi 2016). 3D printing of various dosage forms allows that customized dosages and drug release profiles be designed and manufactured precisely for an individual patient in order to better patient care. 4D printing, as the next step of additive manufacturing, added a new dimension of time to 3D printing and showed unique and significant applications in different fields including drug delivery. Recently, 4D drug products have been introduced following the development of 3D products. In this way, after entering the body, the medicinal product changes its shape under certain conditions, such as water absorption, pH change, and receiving UV rays in order to be more effective over the time. In the topic of drug delivery, the most widely used four-dimensional systems are printed hydrogels and polymers. So far, many studies have focused on the construction of such systems that can release different drugs, including antibiotics and anti-inflammatories, and other drugs in response to a specific stimulus at a desired location (Kuang et al. 2019; Momeni et al. 2017). Combination of 3D printing that is capable of manufacturing personalized drugs and smart materials able to change their own morphology resulted in more and more targeted and effective drug delivery. Therefore, one of the most important parts of 4D printing is smart material. This chapter focuses on drug delivery and manufacturing by means of 4D printing as a cutting-edge technology.

2 3D and 4D Printing

Since 3D printing was first developed by Chuck Hull in 1984, it has been able to open its place among different industries due to its several advantages such as rapid prototyping, complex geometries, material composition, and manufacturing parts directly from computer-aided design (CAD) models. With the passage of time, new additive manufacturing methods were introduced, and now it is possible to print different materials and even composites. In 2013, Tibbitts introduced a new technology of additive manufacturing to the world, at the TED conference, which was intelligently developed by a group of researchers at the Massachusetts Institute of Technology (MIT) (Tibbitts 2019). This new concept, which was developed using the combination of smart materials such as shape memory materials (SMM) and 3D printing, was called 4D printing. In fact, a 4D-printed part can change the shape, property, or functionality of a 3D-printed structure as a function of time (Aberoumand et al. 2021; Rahmatabadi et al. 2022). This concept is illustrated in Fig. 13.1. All the techniques in 3D printing can be used in 4D printing with a few modifications. However, it is very important to choose the right method according to the application. By adding an air circulation system to existing fused deposition modeling (FDM) 3D printing techniques, smart materials can be cooled below low glass transition temperatures. Thus, 3D-printed parts will be able to achieve the shape change required per prediction or for the appropriate application. After minor changes, other 3D printing techniques such as stereolithography (SLA), electron beam melting (EBM), and inkjet printing may also be used. FDM, direct ink writing (DIW), inkjet printing, and digital light processing (DLP) are some other techniques for 4D printing (Raina et al. 2021). The four important parts of 4D printing are smart materials, printing strategies, stimulus, and applications, which are shown in Fig. 13.2. These features of additive manufacturing and 4D printing have made it efficient in the pharmaceutical industry, unlike traditional methods that are limited in some materials and designs and commonly used in the generic form of tablets or capsules with or without enteric coating (Larush et al. 2017).

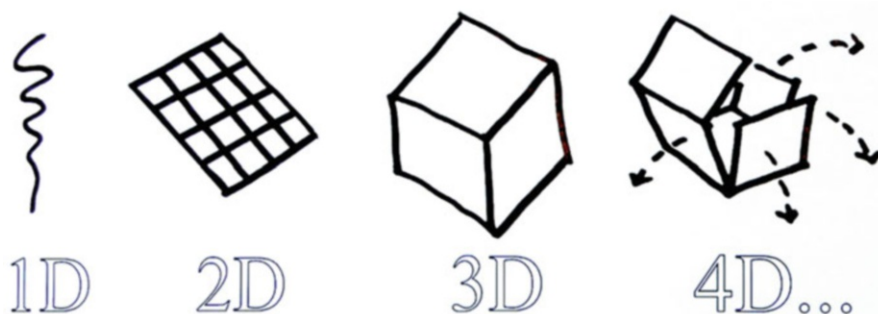


Fig. 13.1 Concept of 4D printing

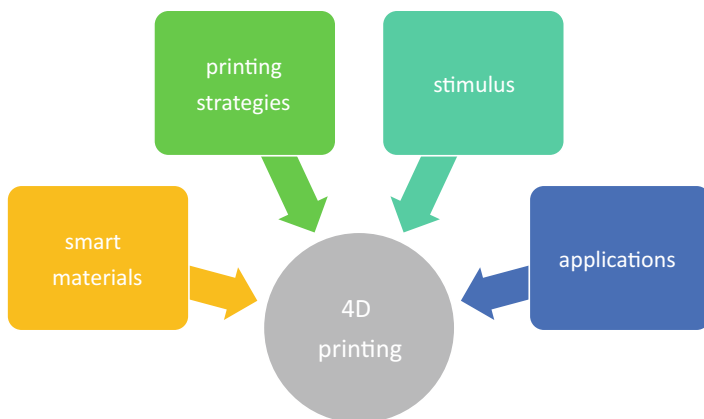


Fig. 13.2 Different aspects of 4D printing

3 Smart Materials and Stimulus

There are different types of smart materials that can be used in 4D printing. Shape memory polymers (SMPs), shape memory alloys (SMAs), shape memory hydrogels (SMHs), shape memory composites, liquid crystal elastomers, and other responsive materials are in a subset branch of smart materials. In the meantime, SMPs and SMHs have received more attention than other smart materials due to their advantages. These advantages include low processing cost, high deformability, excellent medical properties and biodegradability, excellent corrosion resistance, and the ability to be stimulated by various stimuli. Based on the response to various stimuli, smart materials used in 4D printing are briefly introduced below.

3.1 Thermoresponsive Materials

One of the most widely used smart materials in 4D printing is thermoresponsive polymers. All shape memory effect needs to be programmed with a proper condition of trigger. This group of materials changes their shape with temperature stimulation in such a way that they can have a permanent shape at one temperature and a temporary shape at another one. This proper condition of temperature trigger smart polymers can be glass transition temperature (T_g) or melting temperature (T_m) according to its type of mechanism. In general shape, transition temperature (T_{trans}) is known as a proper programming trigger. Shape memory cycle is the most common description of shape memory polymer programming, which includes heating, applying deformation, cooling, and stabilizing the temporary shape and unloading. Figure 13.3 shows the dynamic mechanical thermal analysis (DMTA) shape memory test that includes temperature, strain, and stress too. As it can be seen,

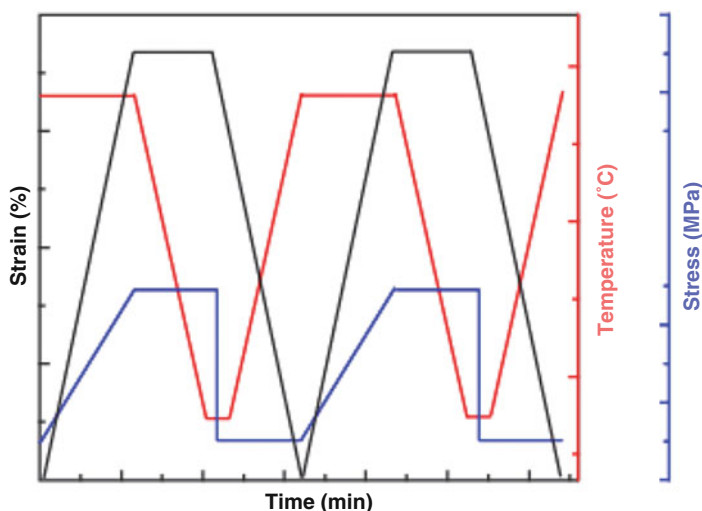


Fig. 13.3 The DMTA shape memory mode plot

initially, temperature rises; then a special strain is applied on the sample; after that, the sample cools down below its transition temperature; and a specific stress and strain is reached. Finally, the sample warms up above its transition temperature, and applied strain and stress are recovered. This shape memory effect program can be repeated for a specific time till the hysteresis unrecoverable strain reaches to a significant amount that the sample loses majority of its elastic energy saving ability.

3.2 *Moisture Responsive Materials*

Water or solution-induced shape memory polymers are another type of thermal stimulation. Due to their special structure, these materials swell by absorbing moisture, and their properties and shape change. The water and solution can act as plasticizer and reduce glass transition temperature under the ambient temperature to occur shape recovery. Another effect of water stimulation is that the hydrogen bonds between molecules expand, particularly in polar polymers, and cause the glass transition temperature to decrease (Salvekar et al. 2017). Some polymers can turn to hydrogel by physical swelling into a solution like water and expand its volume about 200% and show recovery. The most famous materials of this group are hydrogels, which are widely used in biomedical applications. Humidity-sensitive material can be deformed under water and restored to its original shape after drying (Chu et al. 2020).

3.3 Photoresponsive Materials

Light is not a method of direct stimulation for smart materials. In fact, the heat absorbed by light radiation causes the sample to heat up and changes its shape. This behavior makes these materials suitable for 4D printing. Light can change polymer shape by remote induction. Lights with different wavelengths can regulate polymer shape. Because it has no damage to the cells, such as increasing temperature, this stimulus can be used in biomedicine and drug delivery *in vivo* (Chu et al. 2020). Photochemical-induced shape memory polymers have photoactive groups that can make crosslinks when light of a special wavenumber light is applied. Actually, the cross-links that are made during specific light emission can fix temporary shape, and recovery can occur when the wave number alters to a value that photochemical cross-links are eliminated.

Cycloaddition of cinnamate (or coumarin) groups can be employed as a reversible cross-linking switch. As it can be seen in Fig. 13.4, a deformed sample was exposed to UV light ($\lambda > 260$ nm) to promote cycloaddition of the cinnamate groups to form cross-links to fix the temporary shape. Shape recovery could be triggered upon irradiation of UV with $\lambda < 260$ nm, as the result of the cleavage of the cross-links. Despite the photochemical stimulus is attractive, there are some issues about slow recovery rate and poor recovery ratio, and every photo-induced shape memory polymer sample must be very thin, like a film for proper diffusing of emission within the sample. Therefore, its geometry is limited. Molecular mechanism responsible for the light-induced shape-memory is presented in Fig. 13.5.

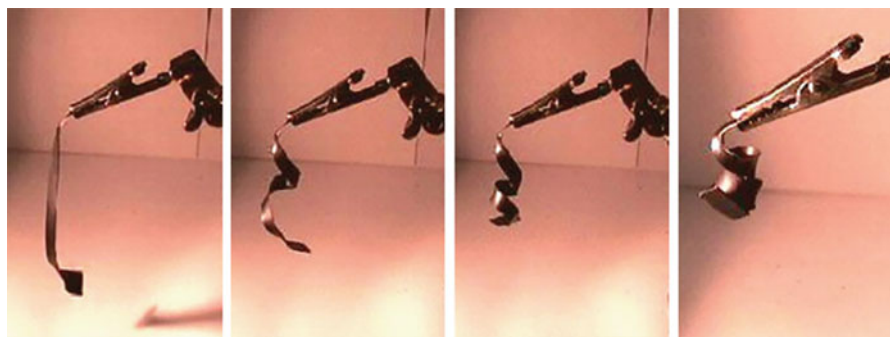
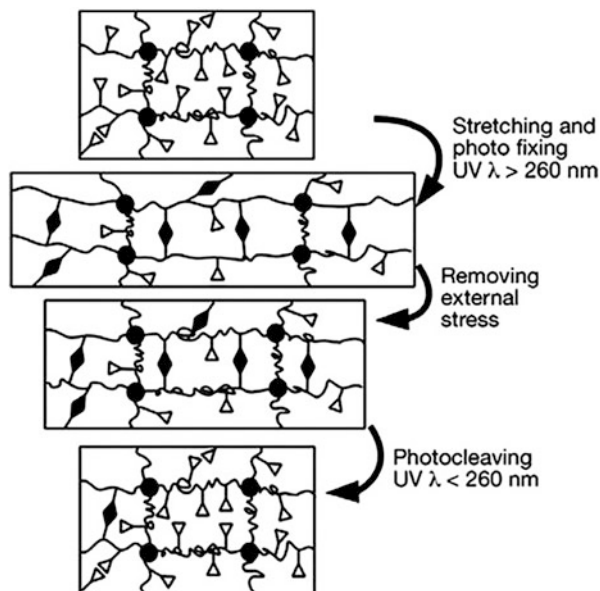


Fig. 13.4 Shape recovery by photothermal-induced shape memory polymers via infrared light emission into a conductive shape memory composite polymer. (Behl and Lendlein 2007; Leng et al. 2011)

Fig. 13.5 Molecular mechanism responsible for the light-induced shape memory. (Lendlein et al. 2005)



3.4 Electroresponsive Materials

In the same manner as light, electricity is an indirect method of stimulating matter, which changes its shape by raising the temperature of the object. For electrical-induced, an electrically conductive filler must be formed into clusters for electron transfer to make Joule heating within the material by applying voltage. This cluster is formed above a specific percentage that is called the percolation threshold. Sometimes, using hybrid fillers with a different geometry or different size scale can be useful for obtaining the percolation threshold with a lower percentage of filler. Figure 13.6 shows the percolated conductive network and percolation threshold. The figure shows that by reaching the percolation threshold, the thermal conductivity must increase dramatically. So, the thermally conductive SMPC especially with carbon-based filler can provide indirect stimulation with high elastic modulus and recovery force.

3.5 Magneto-responsive Materials

Another type of indirect thermal-induced shape memory polymers is magnetic-induced shape memory polymers that are associated with magnetic functional fillers like Fe_2O_3 , Fe_3O_4 , and Ni that can be triggered by inductive Joule heating in an alternating magnetic field for transforming electromagnetic energy from an external high frequency field to heat. The particles inside the material begin to oscillate when

Fig. 13.6 Percolation threshold and conductive network formation concept. (Mukhopadhyay et al. 2014)

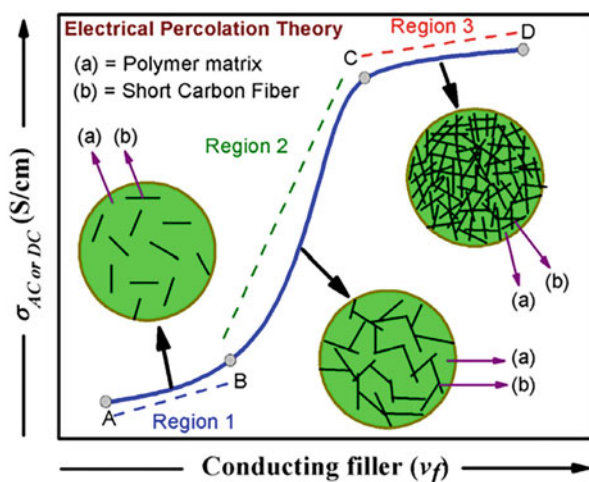
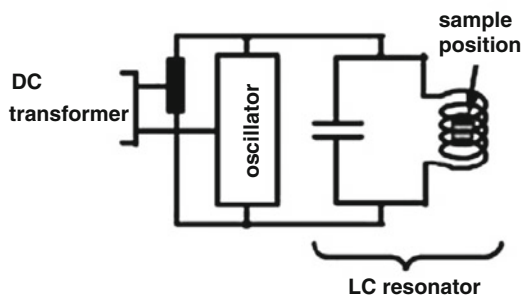


Fig. 13.7 Schematic diagram of the LC resonant circuit-based HF generator used for induction heating experiments and sample positioning for magnetic-induced shape memory polymers. (Schmidt 2006)

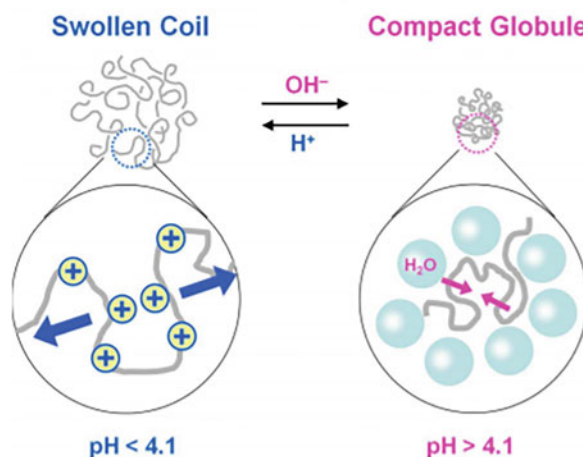


exposed to the magnetic field and cause an increase in the temperature of the object. Composites of shape memory polymers and magnetic particles are a common method for making these materials (Zhang et al. 2019). Magnetic field stimulation is a remote stimulation method with many advantages. Also, a benefit of the magnetic shape memory polymers is that they can be locally and selectively used for special desired recovery procedures. Furthermore, magnetic-induced shape memory polymers are noncontact, so they can be very useful for some special applications, such as biomedical. According to reports, the required magnetic field frequency is around 300 kHz. Figure 13.7 shows the required instrument design for alternative high-frequency magnetic field generation.

3.6 pH-Responsive Materials

It is important to note that these materials behave differently at different pH levels, which make them suitable for 4D printing. By changing the pH, the shape and

Fig. 13.8 Schematic mechanism of pH-induced coil-globule transition for P2VP. At pH below the transition point $\text{pH} \approx 4.1$, intersegment interactions are dominated by electrostatic or excluded volume repulsion, which tends to swell the chain. At pH greater than the transition point, hydrophobic attraction between chain segments tends to collapse the chain into a compact globule. (Melocchi et al. 2019b)



volume of these materials change. As a result, they can be programmed by changing the pH to have different shapes in various environments. pH-sensitive groups, such as amino, carboxyl, and sulfonic, are introduced into polymers to obtain pH-induced SMPs. pH-sensitive switching occurs via hydrogen bond interactions of pH-sensitive groups in the polymer. Globule-to-coil transition can be done in response to changes in PH on the solution in some cases, and the sample turns to coil in lower PH because of excess H^+ due to repulsion; on the other hand, the chain can turn to globule due to attraction. The globule-to-coil transition is shown in Fig. 13.8.

3.7 Piezoelectric Materials

The unique properties of these materials are that they create an electric pulse by changing the stress and change shape when they receive an electric pulse. Due to this property, they can be used in cases that involve electrical stimulation.

4 4D Printing in Pharmaceutics

The innovation process never stops. While 4D printing is just starting to be explored in pharmaceutics (Awad et al. 2018a, b; Trenfield et al. 2018; Zema et al. 2017), 4D printing technology is already starting to take off. As mentioned before, a 4D printing product can alter its morphology independently in response to external stimuli by using time as the fourth dimension. Smart materials are used to change their structure based on light, temperature, water, or pH signals. The use of smart

materials in pharmaceutical formulation has been widely investigated, both as encapsulation techniques for drugs or cells and as bioadhesive devices. Although 4D printing has not yet been applied to pharmaceutical formulation, smart materials have been extensively researched. Therefore, 4D printing applications can be forecast based on the formulation of pharmaceuticals using smart materials. The advent of “smart” personalized formulations might be made possible by combining 3D printing with smart materials that can change their morphology.

In recent years, with the advancement of nanotechnology, a large number of novel drug delivery systems have been designed and built, but the technology of 3D printers created a revolution in this field because it made it possible to build new systems with the same quality and efficiency as conventional systems, which is always a big challenge for scientists in the field of modern drug delivery (Pandey et al. 2020). In the pharmaceutical manufacturing context, the terminology 3D and 4D printing seems to be more acceptable than additive manufacturing, the standard terminology proposed by the American Society of Mechanical Engineers (ASME) (Afzali Naniz et al. 2022). The unique features of the 3D printing process make it suitable for making personalized drugs for each patient in terms of the shape and dose required and the way the drug is released. The one-size-fits-all method is not suitable for all groups of patients, including special patients such as pediatrics, geriatrics, pregnant women, renal impairment, and liver impairment patients (Kavanagh et al. 2018). One of the advantages of the traditional method of drug production compared to 3D printing is its cost-effectiveness and mass production, and the question for the future of 3D printing in the pharmaceutical industry is whether it can meet these standards or not. However, the flexibility and other advantages of 3D printing, including on-site manufacturing, have made it a definite option for entering the future of this industry. Several studies have been conducted in the field of drug delivery systems made with 3D printing, which has shown that this technology is useful in the pharmaceutical industry. There are many review articles in this field of research, and their study gives a wide view of this field (Prasad and Smyth 2016; Beg et al. 2020; Kotta et al. 2018; Trenfield et al. 2019). Table 13.1 shows a summary of some recent studies conducted in the field of drug delivery by 3D printing. This table includes oral, transdermal, ocular, and drug delivery. Further developments related to additive manufacturing have accelerated this process. One of those big steps was the introduction of 4D printing to the world of additive manufacturing technology.

In many researches, shape memory materials have been used in effective and targeted drug delivery. Although 4D printing technology has not been used in these studies, they have facilitated and provided introducing of 4D printing in drug delivery. For example, He et al. suggest a mucoadhesive drug delivery device using pH-sensitive hydrogel that changes its shape when reaches to the small intestine (He et al. 2006). Another pH-sensitive hydrogel for oral insulin delivery was developed by Mukhopadhyay et al. (2014). Li et al. developed a micro-robot by a conventional lithographic technique that has a hydrogel bilayer. One of the layers exhibited pH-responsive properties and aided in drug release by changing its morphology upon exposure to a specific pH. On the other hand, another layer with iron

Table 13.1 Studies conducted in the field of drug delivery with 3D-printed systems

Researcher (year)	Dosage form	Drug	Year	References
Oral dosage forms				
Allahham et al.	Oral disintegrating	Ondansetron	2020	Allahham et al. (2020)
Algahtani et al.	Self-nanoemulsifying tablet	Dapagliflozin	2021	Algahtani et al. (2021)
Yoon et al.	Intestinal	Albumin	2021	Yoon et al. (2021)
Cui et al.	Immediate release	Levetiracetam	2020	Cui et al. (2020)
Serris et al.	Slow release	Paclitaxel, rapamycin, and lidocaine	2020	Serris et al. (2020)
Tan et al.	Sustained release	Theophylline	2020	Tan et al. (2020)
Reddy Dumpa et al.	Delayed release	Theophylline	2020	Dumpa et al. (2020)
Hu et al.	Controlled release	Ketoprofen	2022	Hu et al. (2022)
Erzengin et al.	Sublingual	Insulin	2022	Erzengin et al. (2022)
Schmidt et al.	Intraoral	Triamcinolone	2022	Schmidt et al. (2022)
Transdermal dosage forms				
Economidou et al.	Transdermal microneedle	Insulin	2021	Economidou et al. (2021)
Khosraviboroujeni et al.	Transdermal microneedle	Estradiol valerate	2021	Khosraviboroujeni et al. (2022)
Azizoglu et al.	Transdermal microneedle	Montelukast	2020	Azizoglu and Özer (2020)
Wang et al.	Transdermal microneedle	Cryptotanshinone	2020	Wang et al. (2020)
Lim et al.	Transdermal microneedle	Anti-wrinkle small peptide	2021	Lim et al. (2021)
Teoh et al.	Transdermal wound dressing	Levofloxacin and lidocaine	2022	Teoh et al. (2022)
Xenikakis et al.	Transdermal microneedle	Insulin	2022	Xenikakis et al. (2022)
Li et al.	Transdermal microneedle	Insulin	2022	Li et al. (2022)
Ocular dosage forms				
Naguib et al.	Ocusert	Ganciclovir	2021	Naguib et al. (2021)
Won et al.	Intravitreal injection	Bevacizumab and dexamethasone	2020	Won et al. (2020)
Kojima et al.	Periocular transplant	Brain-derived neurotrophic factor	2020	Kojima et al. (2020)
Kulkarni et al.	Microfluidic device	Dexamethasone	2022	Kulkarni et al. (2022)
Tagami et al.	Patches	Levofloxacin	2022	Tagami et al. (2022)

oxide particles in it enabled the device to be guided magnetically and ensured site-specific drug delivery (Li et al. 2016).

Recent developments in 4D printing technology brought further attention to applying shape memory polymers in drug delivery systems because of their unique ability to alter their shape with various stimuli. This feature makes 4D printing attractive for targeted and controlled drug release. Many studies conducted in this field in recent years, but this field of study has great potential for research because it is a very new topic. One of the pioneer studies in this field was conducted by Larush et al. in 2017. They printed acrylic acid-based hydrogel tablets that are capable of releasing drugs at high pH. That study aimed to evaluate the potential of 3D printing by digital light processing to fabricate drug-loaded systems with special designs and unique drug-release characteristics, which otherwise are not possible to fabricate by conventional pharmaceutical manufacturing methods. In the same year, Okwuosa et al. printed tablets with composite materials as the core and shell of polyvinyl pyrrolidone/methacrylic acid copolymer tablets (Okwuosa et al. 2017). In 2022, hydrogel capsules were made using an injection-based 3D printing technique. These systems had a hydrogel shell made of polyene isopropyl acrylamide, which changed shape and volume in response to temperature. In this way, they could release the drug in their core in a controlled and smart way and become a four-dimensional system (Zu et al. 2022a). The extended release of drugs from stomach-retained systems could be beneficial for many diseases. Melocchi et al. proposed an expandable system for gastric retention relying on the shape memory behavior of pharmaceutical-grade poly (vinyl alcohol) that is developed via 4D printing (Melocchi et al. 2019a). In 2019, Melocchi et al. used hot melt extrusion and fused deposition modeling 4D printing to develop a retentive device for intravesical drug delivery based on the water-induced shape memory response of poly (vinyl alcohol) (Melocchi et al. 2019b). Recently, 3D-printed protein-based hydrogels are developed and applied for programmable structural changes under the action of temperature, pH, or an enzyme. Key to the success of this strategy is the use of methacrylate bovine serum albumin (MA-BSA) as a biodegradable building block for Pickering emulsion gels in the presence of N-isopropyl acrylamide or 2-dimethylaminoethyl methacrylate (Narupai et al. 2021). In a recent study, bio-inspired 4D-printed hydrogels with the ability to create pores due to temperature changes were made using polyene isopropyl acrylamide, which could release the drug by changing the ambient temperature. It was also possible to adjust the pore size and change the speed of drug release in this way (Zu et al. 2022b). 3D-printed micro-robots for targeting the delivery of drugs using the proteolytic degradative property of GelMA, in the presence of collagenase (Wang et al. 2018) and MMP2 enzymes (Ceylan et al. 2019) developed, respectively, by Wang et al. and Ceylan et al. Also a novel gradient four-dimensional printing method toward biomimetic nonuniform, dual-stimuli self-morphing was presented by Song et al. (2020).

5 Conclusion

With the development of additive manufacturing technology and smart compounds, 4D printing has become an increasingly popular means of creating complex structures and valuable devices. Now it is possible to create dynamic and intricate arrangements which were previously impossible using traditional methods. Despite introducing new research avenues because of 4D printing, novel methodologies and materials are still being developed. In pharmaceuticals, this technology is primarily used to create bioadhesion devices targeted at specific patient groups. The formulations are designed to target drug release to specific regions of the GI tract using pH as a stimulus. It appears relatively easy to transition to 4D from 3D printing within the pharmaceutical industry. In response to varying conditions within the gastrointestinal tract, smart materials can be used to create drug delivery technologies that alter and change. Printing techniques, smart materials, and material properties are among the factors that constrain the development of 4D printing processes. Therefore, the field of 4D printing is an interdisciplinary that integrates several disciplines, including the environment, thermodynamics, computer graphics, CAD/CAM, and topology optimization. There is still much development to be done in 4D printing. Even still, science and industry are rapidly entering a revolutionary era. 4D printing will undergo drastic advances in the coming years. By broadening the adaptability, diversity, and use of developed systems, we will be able to advance technologically and scientifically in a distinct field of interest.

Knowledge Assessment

We have designed a number of questions to assess the reader's knowledge improvement after reading this chapter. Thank you in advance for taking the time to fill them out. This evaluation will help the readers to evaluate their learning of the chapter. It should only take 10 min. If you have any questions about these questions, please contact us.

1. What is the fourth dimension in 4D printing?

- Temperature ☐
- Depth ☐
- Width ☐
- Time ☐

2. Which one is the first printed drug?

- Levatipecam ☐
- Ketoprofen ☐
- Triamcinolone ☐
- Dapagliflozin ☐

3. Which one is not one of the stimulants of 4D-printed medicine?

- PH ☐
- Time ☐
- Temperature ☐
- Magnetic field ☐

4. All items are one of 3D printing techniques except...

- SLA ☐
- SLS ☐
- SEM ☐
- FDM ☐

5. All cases are among the applications of additive manufacturing in biomedical except

- Drug delivery ☐
- Tissue engineering ☐
- Implants ☐
- Automotive ☐

6. Which one is not one of the advantages of 3D printing compared to traditional drug production?

- Mass production ☐
- Flexibility ☐
- Personalized dosages ☐
- Low cost ☐

7. What are the most widely used smart materials in 4D printing?

- Electroresponsive polymers ☐
- Magnetoresponsive polymers ☐
- Thermoresponsive polymers ☐
- PH-responsive polymers ☐

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Chapter 14

Characterization Methods of Final Printed Products



D. Rahmatabadi, M. Abedini, A. Bayati, E. Soleyman, I. Ghasemi, M. Baniassadi, K. Abrinia, and M. Baghani

Abstract 4D printing is a new subject in additive manufacturing that is widely used in the medical field and bioprinting. Also, bioprinting innovations have opened new avenues for the transplantation of organs and the regeneration of tissue through 4D bioprinting. Due to the increased attention and applications of printed parts, their biological, mechanical, and microstructural evaluation is a key component. In this chapter, some evaluation methods of biomedical products printed by 3D printing technology have been investigated in the field of tissue scaffolds and drug delivery systems.

Keywords 3D/4D printing · Bioprinting · Evaluation methods · Biomedical application · Drug delivery

1 Introduction

Since 3D printing emerged as a novel and innovative method of manufacturing, it has attracted a lot of attention in the field of manufacturing personalized and customized biomedical devices such as implants, surgical tools, pharmaceutical dosage forms, prosthetics, and many other applications (Midha et al. 2019; Matai et al. 2020; Zhang et al. 2021). 3D printing makes it possible to personalize biomedical devices and manufacture them more rapidly and economically (Murphy and Atala 2014). In order to use biomedical devices safely, one of the requirements of studies and research in this field is to conduct appropriate tests for the biological and pharmaceutical properties of printed products (Omidi et al. 2017; Roeder 2013). The two major fields in biomedical applications where 3D printers has

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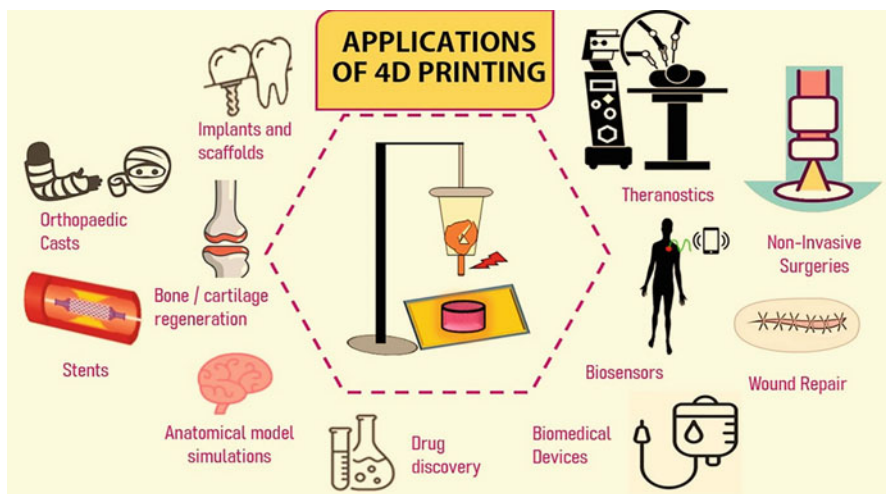


Fig. 14.1 Using 4D printing for biomedical purposes. (Pingale et al. 2022)

revolutionized are tissue scaffolds and drug delivery systems (Joshi et al. 2020). After that, with the expansion of 3D printing and the formation of 4D printing, attention to this field was expanded, especially for bioapplications. 4D printing will have vast applications in the healthcare system and drug design. Due to 4D printing's ability to change shape, the medical industry accepts its use, since this technology is rated as more compatible with the body than rigid metal supports. In addition to improving patient compliance, low toxin levels, low manufacturing cost, and targeted delivery, "smart" drug delivery systems will be fabricated via 4D printing. The healthcare industry is set to be revolutionized by 4D printing in the near future. A 4D printer is a valuable tool for exploring the potential of this technology in the healthcare sector and developing drug delivery systems. Biomaterials at the human scale, tissue planning, and organ printing are just a few of the innovative applications of 4D printing in clinical consideration. Human new developments describe it as being capable of producing biomedical backings, stents, bioprinting, and orthodontic devices (Javaid and Haleem 2019). As a result of the advancement of 4D printing, the monetary, natural, and international implications of producing more substance layers are rising while presenting unparalleled capabilities in interpreting virtual information into distinctive relics in reality (Li et al. 2017). A representation of 4D printing's biomedical applications can be found in Fig. 14.1.

With increasing attention and applications of printed parts, their biological, mechanical, and microstructural evaluation is mandatory and one of the parts that must be addressed. Some evaluation methods of biomedical products printed by 3D printing technology have been investigated in the field of tissue scaffolds and drug delivery systems. Figure 14.2 can demonstrate this chapter at a glance. In this chapter, firstly, bioapplications of 3D and 4D printing will be reviewed, and then their evaluation method will be discussed.

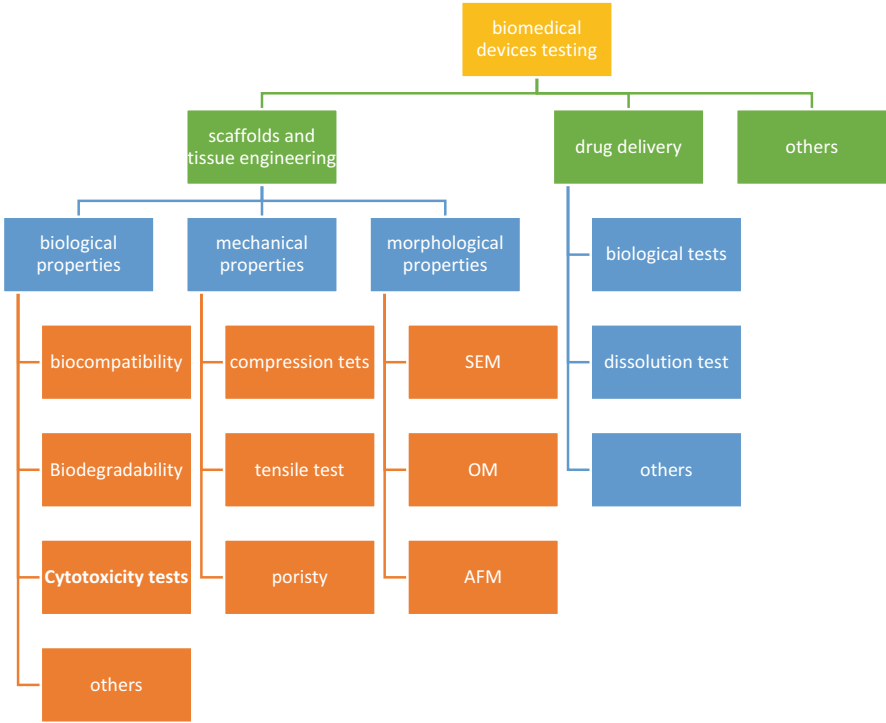


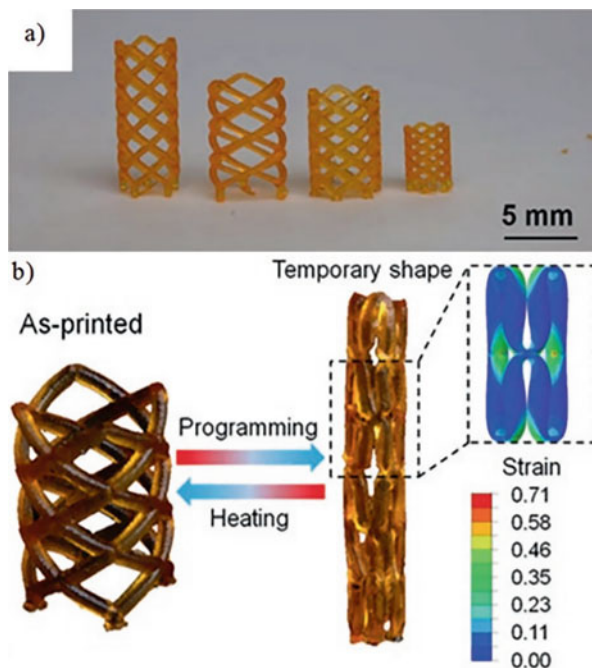
Fig. 14.2 Characterization of biomedical products

2 Tissue Engineering and Bioprinting

Tissue engineering (TE) is a booming field to repair and replace the faulty function of damaged tissue or organs. Nowadays, it is offered as a new treatment, replacing implants, and conventional grafting. It uses biomaterials (scaffolds) and living cells as part of this process. Scaffolding has different meanings in different contexts, but in general, scaffolding refers to a temporary structure that supports the main structure. Scaffolds are often abandoned after the full construction of the main structure. In tissue engineering, a scaffold is a porous artificial framework that serves as mimicry of an extracellular matrix (ECM) for cell adhesion, migration, proliferation, and tissue regeneration in three dimensions (Yang et al. 2001).

Bioprinting innovations have opened novel approaches for the transplantation of organs and the regeneration of tissue through 4D bioprinting. In a study, Miao et al. used the methodology above to develop mesenchymal cells from bone marrow utilizing sustainable soybean oil acrylate (Miao et al. 2016a). The study by Morrison et al. (2015) used bioabsorbable polycaprolactone (PCL) aviation route braces to treat three adolescent patients with tracheobronchomalacia (TBM). Braces can lose their state after some time, and materials eventually decay. This study reveals, if the

Fig. 14.3 (a) Different types of printed cardiovascular stents (b) Changes in stent shape due to temperature variation. (Ge et al. 2016)



support is embedded, it can avoid the discomfort associated with standard treatment. Using epoxidized soybean oil acrylate, Miao et al. (2016b) were able to expand human melanoma stem cells with a shape memory framework using SLA. New shape memory polymers have been developed through the use of PCL triol, castor oil, and multi-isocyanate. A significant improvement in mesenchymal interface microorganisms bonding, expansion, and separation is achieved with these polymers in comparison to PCL.

Using a 4D printer to make stents allows them to be shaped to meet patient needs. A notable recovery in tissue is achieved, as well as the appropriate enhancement of drug meds because it combines boost's reaction effects. Using 4D printing, the doctor will assemble a vein that will spill materials based on the body's temperature (Javaid and Haleem 2020). Conventional fabrication methods are ineffective and time-consuming due to the complex geometry of stents (Fig. 14.3). It is possible, however, to manufacture stents of any size using 3D printing in a time and cost-effective manner using 4D printing. A miniature cardiovascular stent has been designed that can be inserted with minimally invasive techniques by using shape memory polymers (SMPs) (Ge et al. 2016). Stents remain in their larger, clinically effective form after being infused, where they cool and return to their original size. As well as being used to personalize tracheal stents, this mechanism has also been developed for creating so-called smart stents.

An individualized bone recovery can be accomplished with the shape change procedure for sporadic deformities of the bone. Over time, 4D-printed developments may become novel alternatives for bone tissue by adapting to the local microenvironments. The development of new 4D procedures for designing bone tissue has been influenced by reformist methodologies. There have been some improvements in responsive shape polymers that have been thoroughly investigated as hydrogels that can be injectable and used to form bone tissue. In particular, bone abnormalities of varying size and shape may be better addressed by the versatility of 4D-printed bone tissue development. 4D-printed bone tissue development could provide customized bone recovery for those with sporadic bone deformities because of its shape-changing capabilities (Wan et al. 2020).

3 Targeted Delivery Systems for Drugs

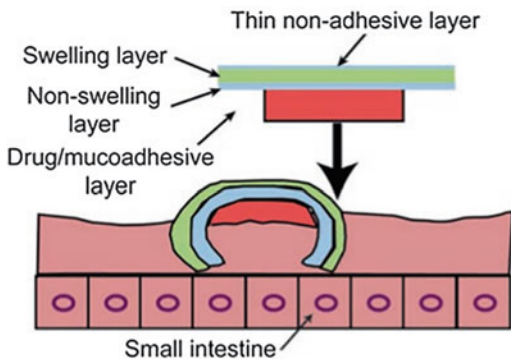
Medication can be delivered to specific parts of the body through targeted drug delivery. The numerous stimuli that 4D-printed devices can provide make them ideally suited to containing pharmaceutical drugs that can be released when the environment at the target site meets the appropriate conditions. Photolithography was used by Azam et al. to fabricate containers. A photoresist panel and thermoresponsive plastic hinge are used to construct the containers, which are made from SU-8 photoresist panels. Figure 14.4 shows different sizes and arrangements of holes in the SU-8 panels for examining how contents are released from the containers (Azam et al. 2011).

A bioprinted medicine delivery device that is directly triggered was developed by Akbari et al. using 4D bioprinting. A combination of alginate fibers and pH-sensitive dye was used to make porous sensors. Recent experiments have been conducted on drug-eluting scaffolds using alginate fibers loaded with gentamicin. The antimicrobial agents were released at the wound site when pH sensors detected a change (Mirani et al. 2020).



Fig. 14.4 The red outline indicates the different patterns of porous faces in these polymeric containers, which are intended for drug delivery. (Azam et al. 2011)

Fig. 14.5 Delivery system for muco-adhesive drugs with three layers. (He et al. 2006; Malachowski et al. 2014)



As well as existing 4D bioprinted systems, other compounds may soon be printed for drug administration. There are few hydrogels that are thermally and mechanically stable. A valve made from hydrogel might close automatically when it comes into contact with hot liquid, therefore drastically reducing poultry mortality. It could someday be used for treating valvular heart disease by replacing damaged valves with prosthetic ones printed by a computer. Hydrogels can be used for the treatment of heart complications or to prevent valve failure (Breger et al. 2015). Researchers worldwide have been exploring the use of 4D printing in drug delivery systems and for materials design since its introduction from additive manufacturing technologies in 2013 (Melocchi et al. 2021). Using 4D printing, objects can be processed beyond complex geometry by giving static printed structures dynamic properties that change over time. As a primary concern, drug delivery systems aim to provide the appropriate amount of therapeutic moieties to the patient's body in the maximum amount of time in order to meet their pharmacological requirements (Maroni et al. 2020). A computational/experimental approach was developed by Inverardi et al. (2021) to fabricate gastro-retentive drug delivery systems using shape memory devices. The glass transition temperature of pharmaceutical-grade plasticized polyvinyl alcohol is close to body temperature.

The endothelium of the intestinal tract is able to adhere to bioadhesion devices, which enables drugs to be released. According to He et al. (2006), they developed a tri-layered, muco-adhesive drug delivery system capable of delivering sustained release formulations (Fig. 14.5). One layer of the device was made of a pH-sensitive hydrogel that, when it reached 6.5 in the small intestine, would contort into a shape that would adhere to the wall of the small intestine.

4 Evaluation Methods

Different types of materials are used for manufacturing scaffolds and other bio-application such as polymers, ceramics, composites, etc. All these printed parts should be tested mechanically, biologically, and morphologically. Some of the following tests should be conducted for testing the scaffolds.

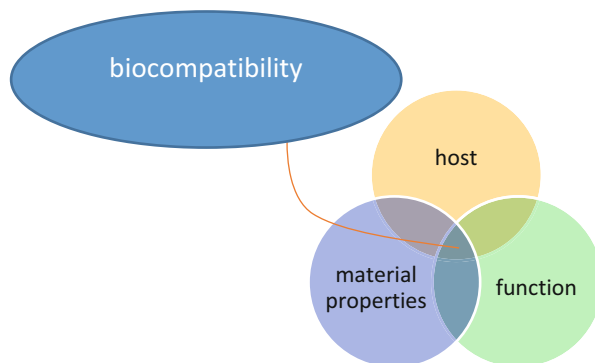
4.1 Biocompatibility

The host response to the printed scaffold and transplanted cells depends on the biocompatibility of the structure. The long-time contact between the implanted scaffold and the recipient tissues implies the need of a rigorous testing program for these scaffolds before clinical application in humans. Before moving on to the clinical application phase of printed scaffolds, it is very important to apply a series of biocompatibility assays in vitro and in vivo (Hussein et al. 2016). In 1998, Williams proposed a great definition of biocompatibility, known as Williams' definition of biocompatibility, described as "the ability of a material to perform with an appropriate host response in a specific application" (Williams 2008). Biocompatibility assessment includes the following aspects: cell compatibility, immune compatibility, as well as characteristics related to the transplantation site and the recipient. These assessments should be conducted based on the rules and guidelines provided by the International Standards Organization (ISO) for testing the biocompatibility of biomaterials for medical applications. Among many assays for the characterization of biocompatibility, in this chapter, cytocompatibility, cytotoxicity, cell viability, and biodegradability are presented (Fig. 14.6).

4.2 Cytocompatibility

Before the clinical use of synthetic bio-tissues and organs, which are essential in reconstructive and regenerative applications, there is an obvious requirement to measure cytotoxicity and cell viability to screen their compositions and determine the potential negative effects of that scaffold. One of the important and influential parameters in measuring implant biocompatibility is cytocompatibility. This parameter evaluates the quantitative and qualitative aspects of the product's effect regarding the cell viability and survival of cultured target cells (Keong and Halim 2009). The International Standard ISO 10993 (International Organization for

Fig. 14.6 Biocompatibility concept



Standardization, 1999) has set a comprehensive guideline on the biocompatibility inspection of materials for biomedical applications with the priority of cell culture-based in vitro assays using both direct contact and indirect contact methods. As stated by the International Organization of Standards (ISO): “The primary aim of this part of ISO 10993 is the protection of humans from potential biological risks arising from the use of medical devices” (ISO 10993-1:2009) (Kejlová et al. 2005).

4.3 Cytotoxicity

The four main reasons why cytotoxicity testing is recommended for all biomedical devices are:

1. Providing the possibility of quick evaluation of samples.
2. Standard protocols are used in these evaluations.
3. The output of these tests is quantitative and comparable data.
4. There is a possibility of discarding biological materials containing toxic matter before further animal tests due to the sensitivity of this test (Ziats et al. 1988).

The term “cytotoxicity” is used to describe a cascade of molecular events that interfere with macromolecular synthesis and cause specific functional and structural cellular damage (Murray et al. 2007). In these tests, the materials extracted from the tested scaffolds are exposed to different cell culture lines. Cell cultures are very sensitive to very small amounts of leachable chemicals and show specific signs of toxicity in the presence of potentially harmful substances instantly (Granchi et al. 1998). The advantage of in vitro tests over in vivo tests has been reported. Therefore, although both systems are needed, in vitro tests are more effective systems for selecting biomaterials. Regarding cytotoxicity inspections, it should be noted that cells cultured in the laboratory (in vitro) are generally more sensitive to toxic substances than in vivo tissues (Cenni et al. 1999). Thus, a substance toxic in vitro may not be particularly toxic to tissues in vivo, whereas a substance harmless to cells is likely to be ineffective in vivo, even in long-term assays. In the cytotoxicity test, it is better to use the same type of cells that encounter the implant inside the body to analyze specific reactions. Therefore, a better simulation of the clinical situation occurs when scaffolds are tested with tissue-derived cells (Harmand et al. 1991). To study general toxicity, cell lines are more widely used than primary cell cultures because, in addition to easy cultivation and insurance of the reproducibility of results, the results are well characterized (Pizzoferrato et al. 1994). There are two recommended testing methods for in vitro cytotoxicity screening:

1. Indirect contact assay
2. Direct contact assay

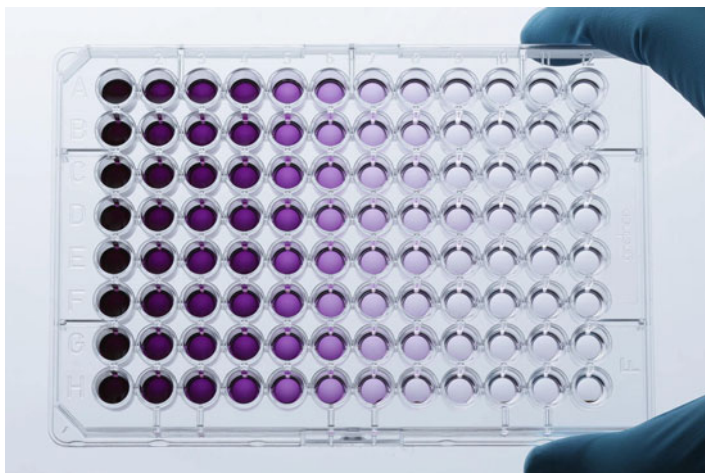


Fig. 14.7 A 96-well plate after the MTT assay. Decreasing amounts of viable and metabolically active cells result in the decreasing intensity of the purple color observed

The MTT test is one of the most commonly used indirect contact assays for assessing cytotoxicity and cell viability. The 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay has become a more common and best standard for the determination of cell viability and proliferation since its development by Mosmann in the 1980s (Mosmann 1983) (Fig. 14.7).

4.4 Biodegradability

The definition of biodegradation is the “breakdown of a substance by enzymes in vitro or in vivo into new compounds.” Biodegradation is very important in modeling and predicting life expectancy after implantation in patients. Accordingly, researchers are interested in investigating the degradation of printed tissues, which can be done in both in vitro and in vivo conditions. The induction of biodegradation in laboratory conditions can be done easily using enzymes (pepsin, trypsin, and bacterial collagenase (Ponce Márquez et al. 2009)) and/or heat and/or acid. However, this method does not mimic the physiological conditions of the host, and accurate information cannot be obtained to predict the lifespan of the scaffold inside the body. In addition, degradation in laboratory conditions is different according to the enzymes used. Therefore, the in vivo method is the best method to check the ability of scaffolds to destroy and regenerate. Also, this method gives researchers the ability to predict cell behavior in the presence of degradation products. Other methods for determining biodegradability are histological and immunohistochemical methods, which are common methods for determining the amount of degradation

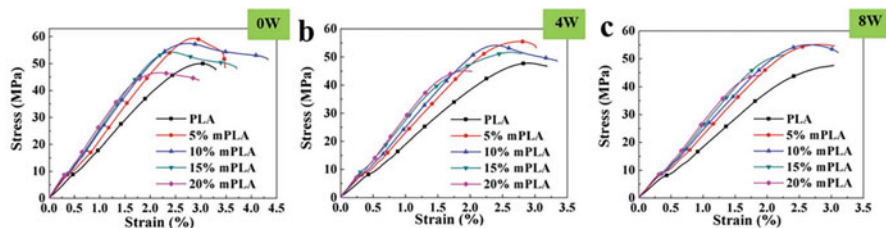


Fig. 14.8 An analysis of the tensile stress–strain curves for shape memory PLA and mPLA composites with different Fe_3O_4 concentrations over different periods of time (37 °C), including 0 weeks, 4 weeks, and 8 weeks. (Lin et al. 2019)

of the scaffold inside the body. But these methods cannot be considered as accurate quantitative methods and cannot provide accurate information about the fate of scaffolds 8.

Biological loads will be experienced by tissue engineering implants after implantation, which means mechanical properties are critical. Lin et al. (2019) used 3D-printed dumbbell-shaped samples to conduct uniaxial tensile tests and determine how the mechanical properties of Fe_3O_4 –PLA composites changed after implantation. The samples were stressed and stretched at body temperature (37 °C) as shown in Fig. 14.8. To determine how mPLA composites perform mechanically with time after implantation, degradation in vitro was characterized to evaluate the effect of degradation on mechanical properties. The uniaxial tensile strength of PBS-immersed samples was determined after predetermined periods of time, using phosphate-buffered saline solution as the tensile test solution. The authors showed that the shape memory poly lactic acid matrix incorporates Fe_3O_4 magnetic particles to allow remote control of occluder deployment after implant. Therefore, 4D-printed shape memory polymer occluders can replace metal occlusion devices.

In another study, Lin et al. (2020) developed two types of shape memory vascular stents with negative Poisson's ratio structures by using 4D printing. Structure optimization was performed using a genetic algorithm. In order to study the mechanical properties of the stents, compression, radial compression, and three-point bending tests were conducted (Fig. 14.9). Additionally, the effect of fluid-structure interaction on stress distribution was investigated employing the finite element method during the shape recovery process. The stents had excellent shape memory effect, and in vitro feasibility tests demonstrated the rapid expansion of simulated narrow blood vessels. As a result, 4D-printed shape memory stents with negative Poisson's ratio structures may hold great promise for treating vascular stenosis.

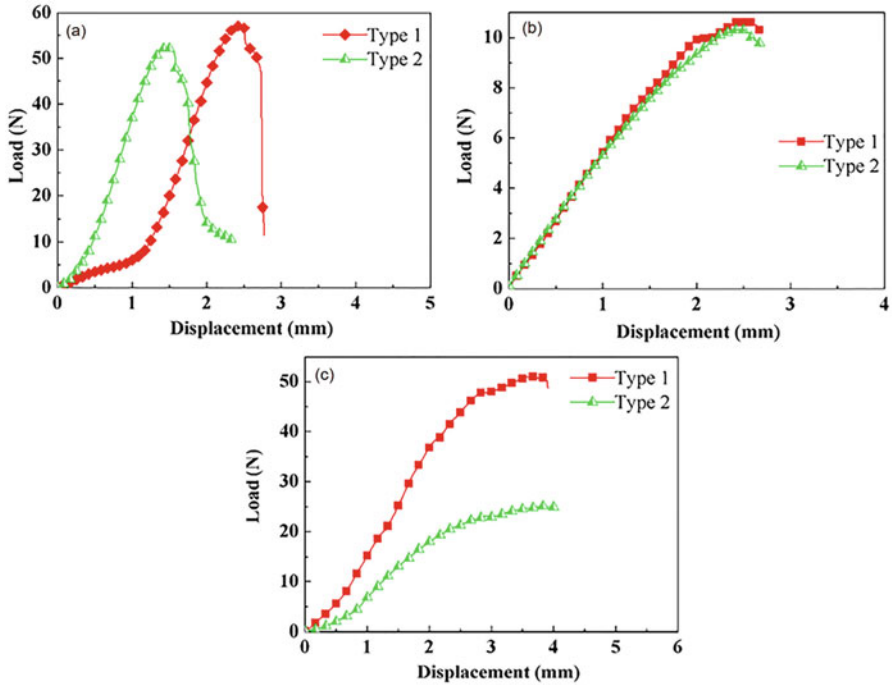


Fig. 14.9 Shape memory stent mechanical behavior. (a) Axial test; (b) radial test; (c) three-point deflection test. (Lin et al. 2020)

4.5 Mechanical Properties

To evaluate the correct functioning of printed scaffolds, mechanical properties tests are performed on them. For this purpose, the usual tension and compression and other mechanical tests are used. One of the important properties of scaffolds is their porosity, which must be checked after construction.

4.6 Porosity

Dense porous structures provide excellent mechanical qualities but poor bone ingrowth. Porous scaffold structures, on the other hand, have a high biological property but a low mechanical strength (Miao and Sun 2010). The porosity of the constructed scaffolds can be calculated by weighing the scaffolds and using Eq. 14.1 (Mi et al. 2013):

$$\text{porosity}(\%) = \frac{V_{\text{th}}\rho - W_m}{V_{\text{th}}\rho} \times 100 \quad (14.1)$$

where W_m is scaffold's measured weight, ρ is material density, and V_{th} is scaffold's volume.

The pore density (N_{cell}) of the scaffolds can be calculated by using Eq. 14.2 (Mi et al. 2013):

$$N_{\text{cell}} = \left[\frac{n}{A} \right]^{3/2} \quad (14.2)$$

where n is the pores' number in the optical image and A is the optical image's area.

4.7 Morphological Properties

The printed scaffolds are subjected to the examination of the microstructure and morphology by scanning electron microscope (SEM), optical microscope, and atomic force microscope (AFM). Also, calculating the pore density (Eq. 14.2) is done with the help of an optical microscope.

4.8 Drug Delivery

In medical science, medicine refers to a substance that is used to treat and relieve symptoms, diagnose, or prevent disease and affects the structure or function of a living organism and corrects the body's function after entering the body. The medicine may have a natural origin (plant or animal), or it may be prepared artificially (chemically). Chemical drugs are usually discovered in the laboratory by doctors or pharmacists, and after sufficient research and approval by official authorities, they are produced in pharmaceutical factories.

Medicines must be stored in special conditions and have a specific dosage and method of use that is determined by the treating physician or pharmacist. Solid pharmaceutical forms are generally divided into the following categories in terms of drug release: immediate release (IR) or modified release.

The form of immediate release takes place in three forms, with the following definitions:

- If at least 85% of the active ingredient in the drug dissolves in 0.1 N HCL medium in less than 15 min, these drugs are called very rapidly dissolving (VRD).
- If at least 85% of the active ingredient in the drug dissolves in the medium in more than 15 min and less than 30 min, these drugs are called rapidly dissolving (RD).

- If at least 85% of the active ingredient in the drug dissolves in the medium in more than 30 min, these drugs are called slowly dissolving (SD).

The modified form of release takes place in two forms:

- Extended-release drugs are drugs in which the active substance is released slowly, and a long time is required for the drug to be released.
- Delayed-release drugs are drugs in which the active substance is released under special conditions in the body, and they require suitable environmental conditions for release (Dash et al. 2010; Kalam et al. 2007; Paarakh et al. 2019).

Generally, controlled-release drug delivery systems involve various methods for controlling the rate of drug release, as well as releasing the drug within a certain time frame and at a specified rate (Weiser and Saltzman 2014).

In order to confirm the quality and quantity of drugs, various tests are performed on pharmaceutical products. There are many tests that must be performed on all biomedical items, including biocompatibility, biodegradability, cytotoxicity, etc. These methods were explained in the previous sections. As new methods of drug manufacture have emerged, such as additive manufacturing and 3D printing, it is necessary to ensure that the type of release of drugs produced through these methods is regulated in the same way as other traditional methods of drug production (Lim et al. 2018). Among the various tests that are performed on medicinal substances, the dissolution test is a sensitive and reliable test as well as a predictor of drug bioavailability in vivo tests.

4.9 Dissolution Test

The dissolution test of pharmaceutical products as a daily quality control test has a decisive role in product quality and has also played an important role in drug development. The dissolution test is a formal test used by pharmacopeias to evaluate drug release from various forms of drugs. Several dissolution apparatuses exist (Cohen et al. 1990; Uddin et al. 2011). In the United States Pharmacopeia (USP), there are five dissolution apparatuses standardized and specified. They are:

USP Dissolution Apparatus 1 – Basket ($37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$)

USP Dissolution Apparatus 2 – Paddle ($37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$)

USP Dissolution Apparatus 3 – Reciprocating Cylinder ($37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$)

USP Dissolution Apparatus 4 – Flow-Through Cell ($37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$)

USP Dissolution Apparatus 5 – Reciprocating Disk ($37\text{ }^{\circ}\text{C} \pm 0.5\text{ }^{\circ}\text{C}$)

5 Conclusion

In this chapter, the evaluation methods of the printed parts are reviewed with a greater focus on bioprinting and 4D printing application. At first, the applications of bioprinting and tissue engineering, which have increased with recent advances in the field of additive manufacturing, were introduced, and then the discussion reached the field of drug delivery. In the second section, characterization methods including mechanical properties and porosity, morphology evaluation, biodegradability, biocompatibility, bio-toxicity, dissolution, and drug delivery tests were fully described and discussed.

Knowledge Assessment

We have designed a number of questions to assess the reader's knowledge improvement after reading this chapter. Thank you in advance for taking the time to fill them out. This evaluation will help the readers to evaluate their learning of the chapter. It should only take 10 min. If you have any questions about these questions, please contact us.

1. Which one is not among the applications of 4D printing in biomedical?

- Wound repair ☐
- Robotics ☐
- Bone regeneration ☐
- Stents ☐

2. Which one is not among the biological properties assay of the printed parts?

- Dissolution test ☐
- Biocompatibility ☐
- Biodegradability ☐
- Cytotoxicity ☐

3. Which one is not used to check morphological properties?

- SEM ☐
- AFM ☐
- OM ☐
- FEM ☐

4. All items are one of 3D printing techniques except...

- Sla ☐
- SLS ☐
- SEM ☐
- ECM ☐

5. The International Standard ISO . . . has set a comprehensive guideline on the biocompatibility inspection of materials for biomedical applications with the

priority of cell culture-based in vitro assays using both direct contact and indirect contact methods.

- 10993 ☐
- 9001 ☐
- 17025 ☐
- 45001 ☐

6. Which of the following is not one of in vitro cytotoxicity tests?

- Direct contact assay ☐
- Indirect contact assay ☐
- MTT ☐
- MMT ☐

7. Which one is not one of the 3D printed drug delivery tests?

- Biodegradability ☐
- Cytotoxicity ☐
- Dissolution test ☐
- Tensile test ☐

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